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Contents on Inside Cover

American Heart Journal

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CONTENTS FOR MARCH, 1944

Original Communications

Clinical Report

Abstracts and Reviews

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Original Communications

THE EFFECT OF CERTAIN SUBSTANCES ON THE INTRAHEPATIC CIRCULATION OF BLOOD IN THE INTACT ANIMAL

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IN A previous study,[1] the distribution and manner of communication of arterial and venous blood within the liver of the intact animal were ascertained by means of the quartz-rod transillumination technique. With the background gained from that work, it seemed advisable to study the effects of various substances, such as glucose, dyes, particulate matter, thyroxin, epinephrine, and acetylcholine, on the intrahepatic circulation of blood in the intact animal by the same method—especially since the literature on the subject revealed a lack of agreement among investigators who had studied by various methods the effects of these substances on the intrahepatic circulation.

METHODS

For studying the effects of various substances on the intrahepatic circulation, the quartz-rod transillumination technique was employed. The frog (*Rana pipiens*) and the albino rat (*Rattus norvegicus*) were the animals used. The observations on the frog were made at room temperature, but those on the mammal were made at animal body temperature by the use of a constant temperature apparatus. The administration of the anesthetic agent, the preparation of the animals, and the exposure of the liver were performed in the manner described in a previous study of the intrahepatic circulation.[1] For fear that the acetylcholine, epinephrine, or glucose might deteriorate on standing, the solutions were prepared freshly before administration.

EPINEPHRINE

Literature.—Fröhlich and Pollak[2] stated that neither concentrated nor dilute solutions of epinephrine have any constrictor effect on the

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portal ramification in the frog's liver. Morita[3] found that a 1:200,000 solution of epinephrine did not have any influence on the caliber of the portal capillaries within the liver. Wertheimer[4] obtained such a sudden and strong effect of epinephrine on the hepatic vessels that the intrahepatic circulation was permanently brought to a standstill, and this could be observed macroscopically. Snyder and Martin[5] stated that the type of reaction of the hepatic vessels of the turtle to epinephrine depends on the pH of the perfusate. Maloff[6] attributed the constriction of the capillaries of the isolated liver of the frog to the epinephrine present in the perfusate. Snyder[7-10] attributed the increased hepatic outflow under the influence of epinephrine to the dilator action of the drug on the hepatic veins, or more probably to the fact that fluid was being suddenly added to the hepatic venous outflow as a result of the giving up of water by the parenchymatous cells of the liver. Schmid[11] showed that epinephrine produces the greatest decrease of the portal blood flow at the moment when it causes the highest rise of portal pressure. He explained the effect as being due mainly to the action of epinephrine on the vessels of the liver. Burton-Opitz[12, 13] showed that epinephrine produces constriction of the ramifications of the hepatic artery and of the portal vein within the liver. Macleod and Pearce[14] studied the effect of epinephrine on the outflow of blood from the liver and attributed the decrease of outflow to the constrictor effect of the drug on the portal ramifications within the liver.

Edmunds[15] obtained an increase of hepatic volume by administering epinephrine intravenously after ligation of the hepatic artery. He attributed the increase of hepatic volume to the damming back of blood in the inferior vena cava. Mautner and Pick[16] found that the effect of epinephrine, either on the intact animal or on the isolated liver, is to produce marked constriction of the hepatic capillaries. Bainbridge and Trevan[17] observed a rise of portal pressure and an increase of hepatic volume after administration of epinephrine. The increase of hepatic volume was attributed to obstruction of the flow of blood from the liver into the systemic circulation. They stated that the most probable cause of the obstruction is a narrowing of the hepatic sinusoids, which is produced by swelling of the hepatic cells. Lamson and Roca[18] stated that the liver is a unique organ whose circulation possesses a constrictor mechanism on the venous side of its capillaries, and that this constrictor mechanism in the dog is under nervous control and can be acted on by epinephrine, which brings about an obstruction of outflow of blood by narrowing the hepatic veins. Loeffler and Nordmann[19] transilluminated the mammalian liver in situ and observed marked paling of the regions under observation whenever epinephrine was applied locally or given intravenously. They attributed the paling to narrowing or complete closure of the capillaries and other vessels in the field of observation.

Lampe[20] suggested that epinephrine causes constriction of only portions of the vessels, possibly the precapillaries, in the perfused liver. Lampe and Mehes[21] observed that epinephrine causes a decrease of hepatic outflow and a diminution of hepatic volume. They attributed these changes to constriction of the vascular ramifications within the liver. Baer and Rössler[22, 23] observed a decrease of hepatic volume when epinephrine was added to the perfusate. They concluded that both the hepatic and the portal ramifications within the liver are endowed with a vasomotor mechanism which is stimulated by epinephrine. McLaughlin[24] noted that the perfused livers of dogs and cats consistently gave a decreased outflow under the influence of epinephrine. The epinephrine was thought to act on the intrahepatic portal radicles. Bodo and Marks[25] found that the addition of epinephrine to the perfused mammalian liver caused a considerable rise of arterial pressure when the epinephrine entered the liver through both the hepatic artery and the portal vein, but, when it was administered only through the portal route, the rise of arterial pressure was less marked than when it was administered by both routes. Clark[26] observed a rise of portal pressure in the intact cat and a considerable decrease of hepatic volume and perfusion flow under the influence of epinephrine. He explained the rise of portal pressure and the reduction of perfusion flow as due to the constrictor action of epinephrine on the intrahepatic vessels, and not to swelling of the hepatic cells. Mattson[27] observed a rapid and pronounced decrease of hepatic volume in every experiment in which epinephrine was administered intravenously.

Grab, Janssen, and Rein[28, 29] found that giving small doses of epinephrine intravenously caused the hepatic outflow to exceed the inflow to such an extent that about 59 per cent of the weight of the bloodless liver might be lost during the period of excess outflow. They suggested that epinephrine relaxes the efferent hepatic veins. Carnot, Gayet, and Merklen[30] consistently observed elevation of portal pressure after injection of epinephrine. The rise of pressure was attributed to the constrictor effect of epinephrine on the arterioles in the portal regions. Griffith and Emery[31, 32] attributed the decrease of hepatic volume to the asphyxial secretion of epinephrine which caused constriction of the intrahepatic vascular ramifications. They observed a decrease of hepatic volume when epinephrine was administered into the hepatic artery. By means of the Rein thermostromuhr, Schwiegk[33] observed an increase of flow in the hepatic artery when small doses of epinephrine were given in the form of continuous infusions, but the plethysmographic record of hepatic volume gave variable results—sometimes an increase, at other times a decrease. With the administration of epinephrine, Bauer, Dale, Poulsson, and Richards[34] observed constriction of the ramifications of both the hepatic artery and the portal vein. They stated that epinephrine opens the sluice mechanism located near the openings of the hepatic veins into the inferior vena cava. McMichael[35] observed a decrease of

hepatic volume when epinephrine was administered. He suggested that the constrictor effect of epinephrine must be on the portal venous ramifications in the liver, and not on the sublobular hepatic veins.

Rüegg[36] found that, in the perfused liver of the dog, epinephrine might cause either an increase of outflow by producing diminished portal resistance, or a decrease of outflow accompanied by a rise of portal resistance. Pak and Read[37] compared the effect of ephedrine with that of epinephrine on the hepatic circulation of dogs and cats. Ephedrine caused a prolonged rise of the portal pressure of dogs, but the rise was not as marked as that produced by epinephrine. The rise of portal pressure was attributed to vasoconstriction of the portal ramifications. Tschernogoroff and Popoff[38] perfused the liver of the dog in situ, and observed a decrease of hepatic volume and a rise of portal pressure on administration of epinephrine. With large doses of epinephrine, Katz and Rodbard[39] observed a rise of portal pressure and a sharp decrease of portal flow, followed sometimes by an increase, with a final return to the control level; but in small doses the portal flow may increase while the venous pressure falls. Chakravarti and Tripod[40] noted the following three actions of epinephrine on the perfused liver: (1) the sluice mechanism at the entrance of the hepatic veins into the inferior vena cava was opened, thus removing the resistance on the venous side and decreasing the volume of the liver; (2) the resistance on the inflow side was increased by constriction of the ramifications of both the hepatic artery and the portal vein in the liver; and (3) when the epinephrine already in the perfusate caused a decrease of hepatic volume, the added epinephrine caused an increased resistance on the outflow side. Sympathomimetic drugs—tyramine, ephedrine, veritol, sympatol, and benzedrine—acted like epinephrine except that their effects were much more prolonged.

Results.—A. Observations on the amphibian liver: One-tenth cubic centimeter of a 1:10,000 to 1:100,000 solution of epinephrine hydrochloride, when administered intravenously, or the direct application of a drop over the region under observation, repeatedly caused constriction of the sinusoids of the liver, regardless of whether they were arterial, portal, or hepatic venous. The time which elapsed between the administration of epinephrine and the constrictor effect on the sinusoids of the liver was brief; it varied between five and ten seconds. The duration of the constrictor effect was roughly proportional to the concentration of epinephrine administered. However, the arteriovenous anastomoses, as well as the points of origin or bifurcation of the vessels, were affected most conspicuously. When the lower dilutions were used, the arteriovenous anastomoses constricted to the point of disappearance, and most sinusoids in the region under observation contracted to such an extent that the individual corpuscles were squeezed tightly into single file in the lumen. When higher dilutions of epinephrine were administered, the arteriovenous anastomoses contracted slightly, but the force

of arterial flow was so strong that blood was pushed in both directions through the vein at the anastomoses and reversed the direction of flow distal to the arteriovenous anastomoses. The flow in both directions in the vein at the arteriovenous anastomoses lasted for more than two minutes, and the sinusoids draining into that vein became efferent sinusoids; that is, they carried blood away from that vein into the lobule which they traversed, instead of draining it into that vein as they did before the administration of epinephrine. After the constrictor effect of epinephrine wore off—which was usually within three minutes, except in the case of very low dilutions, in which it lasted a little longer—there followed a gradual reactivation of the whole lobule, with engorgement of the sinusoids by the packed corpuscles in the rapidly flowing stream through their lumina. At this stage the arteriovenous anastomoses were wide open, and the reverse flow increased to such an extent that it completely overcame the draining stream and made of the whole region a supplying instead of a draining system.

Direct application of a drop of 1:10,000 solution of epinephrine hydrochloride caused, in addition to the constriction of the sinusoids and arteriovenous anastomoses, shrinkage of the hepatic lobule to such an extent that the region under observation pulled away from the objective of the microscope.

B. Observations on the mammalian liver: Solutions of 1:10,000 to 1:100,000 epinephrine hydrochloride, when administered in amounts of 0.1 c.c. into the portal vein or the inferior vena cava, or two drops applied directly through a fine needle over the illuminated region, repeatedly produced a constrictor effect on the sinusoids of the liver, regardless of whether they were arterial, portal, or hepatic venous, or whether they were located in the periphery or center of the lobule. The constrictor effect produced by direct application of epinephrine appeared within ten seconds and lasted two to four minutes, after which, reactivation of the sinusoids took place gradually. With the higher dilutions the reactivation of the constricted sinusoids was accompanied by activity of the sinusoids that were inactive in the field under observation prior to the application of the drug. When the more concentrated solutions were applied, the region became very much blanched with almost total disappearance of corpuscles from the extremely contracted sinusoids during maximal constriction; and, as the effect of the drug wore off, not all of the sinusoids became reactive. The duration and the degree of blanching varied roughly in proportion to the concentration of the solution of epinephrine which was applied.

Of the two intravenous routes of administration, that by way of the portal vein gave a much more lasting and a stronger constrictor effect than that by the caval route. The constrictor effect produced by the injection of epinephrine into the inferior vena cava lasted, invariably, less than four minutes, and rarely appeared before ten seconds after the injection. Injecting the same amount and dilution of epinephrine

into the portal vein caused, within five seconds, marked constriction of the sinusoids under observation, and more than four minutes elapsed before activity became as it was prior to the injection. When the contracting sinusoids trapped corpuscles in their lumina, the constrictor effect of epinephrine seemed more conspicuous at the point of entrance of the sinusoids into the draining veins, which was the only region where no lumen could be discerned during the effect of epinephrine. On several occasions erythrocytes were seen outside the lumen of the sinusoid, between it and the bordering hepatic cells. This seems to indicate the presence of regional deficiencies in the walls of sinusoids.

It was observed that when the drug was administered into the inferior vena cava the constrictor effect was replaced within four minutes by overactivity of the circulation in the whole liver, both as to number of active sinusoids and as to engorgement and rate of flow of blood in them. More than twenty minutes elapsed before the activity subsided to the preinjection state. The effect of epinephrine on the anastomoses between the ramifications of the portal vein and the hepatic artery in the periphery of the lobule was also studied. The ramifications of both the portal vein and the hepatic artery were narrowed considerably for more than one minute, and the communications between them disappeared until the constrictor effect wore off, after which each anastomosis looked much larger than it was prior to the injection of epinephrine.

ACETYLCHOLINE

Literature.—Snyder[7-10] showed that a vagus stuff is liberated into the perfusate of the isolated liver of the turtle as a result of stimulation of the vagus nerve. He also demonstrated that acetyl-β-methylcholine increases the rate of outflow from the liver when the pH is 7.0, and decreases it at a pH of 7.5. In another publication, he attributed the reduction of hepatic volume to the decrease in portal inflow caused by the vasoconstrictor effect of acetyl-β-methylcholine on the portal venous bed. He stated that the cholinergic drug, as well as the impulses of the motor vagal nerve, produces constriction of the hepatic venous sphincters. In his latest publication, Snyder[9] explained the effects of cholinergic drugs as being due to peristaltic constriction of the hepatic venules and the hepatic vein, without active participation of the hepatic sinusoids. Hunt[41] stated that acetylcholine has a dilator action on the terminations of the hepatic artery, and that this effect disappears when the artery is ligated. Bauer, Dale, Poulsson, and Richards[34] found that acetylcholine had hardly any perceptible effect on the ramifications of the hepatic artery or of the portal vein. McMichael[35] stated that, with large doses of acetylcholine, he obtained constriction of the portal branches and a rise of portal pressure. Katz and Rodbard[39] noted that acetylcholine in amounts up to 10 micrograms did not have any effect, but in doses of more than 100 micrograms it produced a fall of the portal and arterial pressures and a decrease of

portal flow. When Chakravarti and Tripod[40] injected acetylcholine into the portal vein, they did not observe any increase of hepatic volume, but when the drug was injected into the hepatic artery, the increase of hepatic volume was attributed to increased arterial flow and to diminution of outflow.

Results.—A. Observations on the amphibian liver: Solutions of 1:100,000 to 1:10,000,000 of acetylcholine bromide were applied directly to the region under observation or injected into the vein leading to the liver. Neither by direct application nor by intravenous administration were any observable effects produced on the circulation in the liver: the sinusoids did not show either constriction or dilatation. The arteriovenous anastomoses in fields under observation were also unaffected by the acetylcholine. However, at times, after the acetylcholine reached the heart, the liver became temporarily congested from stasis of the blood in the sinusoids produced by the transient "standstill" of the heart which was brought about by the parasympathomimetic drug.

B. Observations on the mammalian liver: Solutions of 1:10,000 to 1:10,000,000 of acetylcholine bromide were administered either by direct application to the region of the liver under observation or by injection into the portal vein. Neither by direct application nor by intravenous administration were any observable effects produced on the circulation of the intact liver: the sinusoids did not show either constriction or dilatation. In two experiments, there was one arteriovenous anastomosis in the interlobular margin. The acetylcholine did not have any effect on the anastomosis in either case. When the higher concentrations were administered, the drug slowed the heart, and, as a result, slowing of the flow in the sinusoids and some engorgement followed. In some experiments the heart stopped for about fifteen seconds, during which there were real engorgement of the liver and stasis in the sinusoids. However, the activity of the sinusoids returned to the preinjection state as soon as the heart began beating vigorously after the effect of the parasympathomimetic drug wore off. A few experiments were tried with very large doses of acetylcholine (0.3 c.c. of 1:1,000 solution), administered into the portal vein. An immediate but transient constriction of the portal branches was observed.

GLUCOSE

Literature.—Mautner[42] observed a long-lasting increase of hepatic volume after intravenous administration of glucose, levulose, and maltose. He suggested that the lysis water released during the formation of glycogen from these sugars is the probable cause for the increase of hepatic volume. Mattson[27] found that glucose or levulose, when given intravenously, produced definite increases of hepatic volume which were greater than those produced by the injection of equivalent amounts of physiologic saline solution. After the intravenous in-

jection of 20 c.c. of a 40 per cent solution of glucose, Schwiegk[33] found that the blood flow in the hepatic artery increased to double the control volume, whereas the portal flow increased 10 per cent. Lichtwitz[43] expressed the belief that there is a "functional coordination between the chemism of the liver and its circulation." Free hepatic circulation assures the delivery of dextrose to the consuming organs.

Results.—A. Observations on the amphibian liver: Slow intravenous injection of 1 c.c. of a 10 per cent solution of glucose per 25 Gm. of frog body weight produced an increase in the circulatory activity of the liver. This observation was confirmed repeatedly in different lobules of the liver of the same animal and in the livers of different animals. For example, in one region under observation, twenty-eight sinusoids were inactive, but contained motionless corpuscles in their lumina before injection. Six minutes after the slow injection of 1 c.c. of a 10 per cent solution of glucose, twenty-three sinusoids became active, and before the end of ten minutes no inactive sinusoids were seen in the field. This increase of activity continued for more than two hours. Sufficient observations have been made, and all showed that when glucose is slowly administered intravenously it increases the circulatory activity in the hepatic lobules. Under similar conditions, control experiments were performed by substituting the same quantity of frog Ringer's solution for the glucose. No noticeable increase of circulatory activity in the liver was manifested in the controls.

B. Observations on the mammalian liver: Slow intravenous administration of 1 c.c. of a 10 per cent solution of glucose in Ringer's solution per 50 Gm. of rat body weight led within three minutes to a gradual increase of circulatory activity in the liver. Before the lapse of fifteen minutes after the injection, practically all the hepatic lobules and their sinusoids were in full circulatory activity. The lobules or portions of lobules that were active prior to injection continued in full activity, and those that were inactive became active. Even the short transverse and oblique sinusoids which connect the radial ones became patent and fully active. This marked increase of circulatory activity lasted more than two and a half hours, after which a gradual return to the preinjection state was observed. Under identical conditions, control experiments were performed by substituting Ringer's solution without glucose. No perceptible change in the circulatory activity of the livers of the control animals could be observed.

THYROXIN

Results.—A. Observations on the amphibian liver: Daily injections of 1 mg. of thyroxin into the dorsal lymph sac for a period of ten to twenty days, or the feeding of thyroid for the same period produced a great increase of circulatory activity in the liver. To the naked eye the exposed livers appeared much redder than those of the controls. Microscopic examination of the transilluminated liver in situ showed

that practically all the lobules were in the active state, in contrast to the controls, in which the majority of the livers were comparatively inactive. There were many more patent arteriovenous anastomoses between corresponding branches of the portal vein and the hepatic artery, and of the hepatic artery and the hepatic vein, and also many more regions of sinusoids supplied with arterial blood in the livers of frogs to which thyroxin or thyroid had been administered than in the controls. Three per cent of the frogs died during the period of administration, and two per cent did not show any noticeable increase of circulatory activity in their livers. All the others manifested the described changes of their hepatic circulation, plus a loss of weight ranging from 2 to 8 grams.

B. Observations on the mammalian liver: Daily subcutaneous injections of 0.05 to 0.1 mg. of thyroxin per 50 Gm. of rat body weight over a period of ten days caused a marked increase of circulatory activity in the liver. From the second day, the liver began to look hyperemic, and, on microscopic examination, a slight increase of circulatory activity was observed. About the sixth day of administration of thyroxin, the increase of circulatory activity in the liver attained its maximum, during which there was complete activity of all sinusoids of the liver. The intermittence, or shift, of circulatory activity that was observed in the control livers was no longer present under the influence of thyroxin. There were scarcely any sinusoids or portions of lobules which could be considered in the resting phase. Even the oblique and transverse sinusoids were active, and the whole liver pulsated from the increased circulatory activity. Arteriovenous anastomoses in the interlobular spaces between the hepatic artery and the portal vein were observed more frequently in livers of rats which received thyroxin than in the controls.

After the administration of thyroxin was stopped, the circulatory activity in the liver took about two weeks to subside to the normal state and show the intermittence and alternation that were observed in the hepatic circulation of the control rats from the same litter.

PARTICULATE MATTER AND DYES

Results.—A. Observations on the amphibian liver. India ink: Injection of 0.2 c.c. of a 1 per cent suspension of India ink into the lymph sac, within a period of five to twelve minutes, led to a gradual increase of circulatory activity in the hepatic lobules. Within forty-five minutes there remained practically no region of the liver in which the circulation was not active. Almost every sinusoid was patent, and blood was rapidly coursing through it, with many particles of ink carried in the stream. Many arteriovenous anastomoses became patent. At the same time the reticulo-endothelial cells of Kupffer gradually became loaded with particles of ink. After about two hours from the time of injection, the Kupffer cells became so loaded with black particles

that the whole liver became extremely dark. At this stage the circulation of the liver became much less active than before, and many sinusoids were observed in various phases of inactivity. The Kupffer cells were seen in the walls of the sinusoids, and were located most commonly at the bends. Often Kupffer cells loaded with particles of India ink were seen projecting into the lumen of a sinusoid, but they were never seen in the lumen of a sinusoid with strands connecting them to the wall.

Dyes: The intravenous administration of 0.05 c.c., or the injection into the lymph sac of 0.2 c.c. of a 1 per cent solution of methylene blue, or of gentian violet, led in a few minutes to a marked increase of the circulatory activity in the liver which continued for more than three hours. The regions in which sinusoids had been in various stages of inactivity before the dye was injected became so active that practically every sinusoid was opened, with blood rapidly coursing through it. Under the influence of the dye no increase in the number of patent arteriovenous anastomoses in the regions under observation was noticed.

B. Observations on the mammalian liver. India ink: Injection of 0.1 to 0.2 c.c. of a 10 per cent suspension of India ink in mammalian Ringer's solution into the inferior vena cava led, within two minutes, to a gradual increase of circulatory activity in the liver. Within ten minutes practically every lobule in the liver was active, and the sinusoids were filled with blood and particles of ink which rapidly streamed through them. Thereafter, the reticulo-endothelial cells of Kupffer became evident by the presence of particles of ink within them. Observations were made for periods extending over six hours. No matter how dark the liver became, or how loaded the Kupffer cells were with particles of ink, the circulation remained active. It was repeatedly observed that the regions where the supply to the sinusoids was mainly arterial had the least number of Kupffer cells, and these were comparatively very slightly charged with particles of ink. Four or five sinusoids fed by ramifications of the hepatic artery could be traced all along their course toward the central vein, and no charged Kupffer cells could be detected in their lumina or in their walls, whereas, in the walls of the sinusoids supplied by the comparatively slower stream from the portal vein, many Kupffer cells could be observed and were loaded with particles of ink. Some of these charged Kupffer cells bulged into the lumen, and others were within the lumen, and connected to the wall by strands over and under which erythrocytes passed through the sinusoids.

SUMMARY

The effects of glucose, dyes, particulate matter, thyroxin, epinephrine, and acetylcholine on the intrahepatic circulation of blood in intact animals were studied in vivo by means of the quartz-rod transillumination technique. Glucose increased the intrahepatic circulatory activity. Particulate matter, India ink, and dyes increased the intrahepatic circu-

latory activity and stimulated the phagocytic action of the Kupffer cells. The Kupffer cells became loaded with particles shortly after the injection of India ink. In the frog no Kupffer cells were seen within the lumina of the sinusoids, whereas in the rat such cells were found within the lumina of the sinusoids and were connected by strands to the sinusoidal wall. Thyroxin caused an increase of the vascular activity within the liver to such an extent that one could rarely find any sinusoids in the inactive phase. Epinephrine produced blanching of the liver by causing constriction of the intrahepatic vascular ramifications, but acetylcholine did not have any preceptible vasodilator effect.

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AURICULOVENTRICULAR BLOCK WITH VENTRICULOAURICULAR RESPONSE

Report of Six Cases and Critical Review of the Literature

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EXPERIMENTS on animals have shown that retrograde conduction is a normal function of the muscular conduction system.[1] Clinical experience, however, is not quite in accord with the experimental results, as this report will illustrate.

When A-V nodal rhythm is established by the action of a lower rhythm center which forms impulses at a more rapid rate than the sinoauricular pacemaker, block of the V-A (retrograde) conduction, giving rise to a complete or incomplete A-V dissociation,* is observed far more frequently than retrograde conduction, giving rise to a true A-V nodal rhythm of the whole heart. Retrograde conduction of the impulse in the case of ventricular extrasystoles occurs even less frequently, and retrograde conduction in which idioventricular rhythm arises below the bifurcation of the common bundle rarely occurs.

It is therefore surprising that retrograde response should occur, and show a normal or almost normal transmission time, when orthograde conduction is grossly impaired. We have been able to find nineteen such cases in the literature. Three further cases of our own are presented, together with three additional cases which were kindly put at our disposal by Dr. Louis N. Katz and Dr. John Parkinson.

CASE REPORTS

Case 1.—A woman, 62 years of age, with long-standing hypertension. An attack of dizziness without loss of consciousness, in July, 1937, was followed by a bradycardia of 35 beats per minute and a fall of the systolic pressure from 210 to 140. No drugs had been given prior to the attack, and there had been no complaints of anginal pain. The condition remained stationary for the whole time of our observation (over two months).

Electrocardiograms (six records on four nonconsecutive days within seven weeks).—

A. Sept. 11, 1937 (Fig. 1, *A*). There is complete A-V block, with idioventricular rhythm; the latter probably arises below the bifurcation of the bundle of His, at a regular rate of 37. There is "low voltage"; the QRS duration is 0.13 second. The sinus rhythm is

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*The term A-V dissociation is used in contradistinction to A-V block to indicate independent action of auricle and ventricle, not the result of impaired A-V conduction but resulting from the normal refractory period of the junctional tissue when the rate of the subsidiary pacemaker exceeds that of the sinus impulses transmitted to the subsidiary pacemaker.

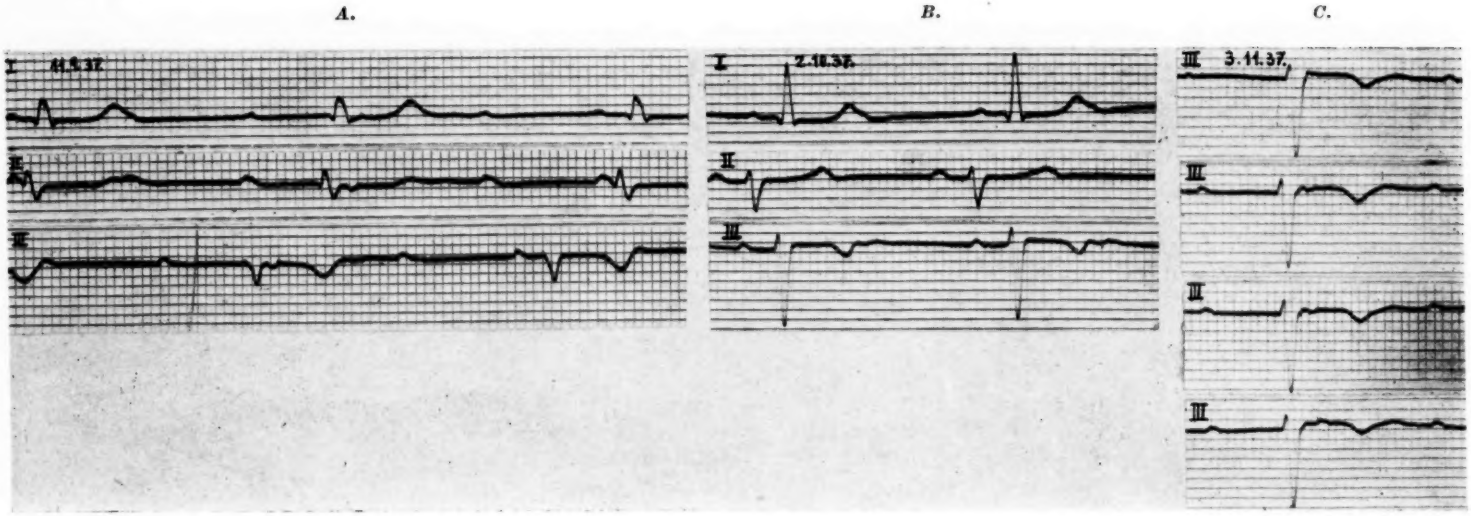

Fig. 1.—Case 1.

A, Complete A-V block with preserved V-A conduction. The fourth auricular deflection in Leads I and II and the third P in Lead III are retrograde responses. The retrograde P is upright in Lead I and inverted in Leads II and III.

B, Three weeks after *A*; 2:1 response. No retrograde P waves.

C, Four weeks after *B*; four idioventricular beats of supraventricular origin. The occurrence of retrograde P waves depends upon the length of the preceding P-R. Only the two middle tracings show retrograde conduction as evidenced by premature and inverted P waves after the QRS. In the upper tracing, retrograde conduction fails because P-R is too long and the normal orthograde P supervenes, whereas, in the lower tracing, retrograde conduction fails because P-R is too short and the retrograde impulse is blocked.

Time intervals = 0.05 second; 1 millivolt = 1 cm.

slightly irregular because of the varying position of P in relation to the ventricular complex; the P-P intervals which include a ventricular beat are shorter than the P-P intervals which do not.

The fourth auricular beat (P′) in Leads I and II and the third in Lead III are definitely premature. Each follows R by an interval of 0.15 second, is upright and small in Lead I, and inverted in Leads II and III. The following interauricular interval (P′-P) is lengthened and compensates for the shortening of the preceding P-P′. Whenever P-R is within the limits of 0.415 to 0.450 second, a similar arrhythmia occurs. When P-R is under 0.410 second, or above 0.550 second, the subsequent P is normal in shape and occurs at the expected time. Within the range for P-R of 0.460 to 0.550 second, P′ occurs within the limits of normal P-P intervals or is slightly premature. It differs from the other P′'s in not being inverted in Leads II and III, and also differs from the normal P in minor details; however, its shape is difficult to recognize because of the superposition on T.

As shown, the premature auricular beats represent ventriculoauricular responses. The intermediate character of responses in late auricular diastole is produced by the fusion within the auricles of the normal sinoauricular impulse with the retrograde impulse. Such beats, resulting from simultaneous stimulation of the same portion of the heart by two impulses, might be termed "fusion beats,"[2] in contradistinction to beats showing "superposition" in the electrocardiogram, i.e., algebraic summation of electrograms of various portions of the heart stimulated simultaneously.

B and C. Sept. 18, and Oct. 2, 1937 (Fig. 1, *B*). There is 2:1 auriculoventricular response throughout, and sinus arrhythmia with alternation of the P-P intervals; those which contain a ventricular complex are shortened. This is common in A-V heart block, and we propose to call it "ventriculophasic sinus arrhythmia in heart block."

D. Nov. 3, 1937 (Fig. 1, *C*). There is a high-grade, incomplete A-V block; the ventricles are controlled for the most part by an idioventricular pacemaker, and orthograde impulses are transmitted only in late ventricular diastole. When R-P exceeds 1.58 seconds, the R-R of the idioventricular rhythm measures 1.92 seconds, and conduction takes place with a P-R of 0.22 to 0.26 second. Idioventricular and conducted ventricular complexes differ only in minute details, and are

TABLE I

REFRACTORY PERIOD FOR ORTHOGRADE (A-V) AND RETROGRADE (V-A) CONDUCTION IN CASE 1

DATE	RHYTHM	ORTHOGRADE CONDUCTION			RETROGRADE CONDUCTION		
		P-R	LONGEST R-P NOT FOLLOWED BY CONDUCTION	SHORTEST R-P FOLLOWED BY CONDUCTION	R-P′	LONGEST P-R NOT FOLLOWED BY CONDUCTION	SHORTEST P-R FOLLOWED BY CONDUCTION
9/11/37	Complete A-V block, idioventricular rhythm	∞	1.37		0.15	0.41	0.415
9/18/37	2:1 A-V block	0.205	0.54	1.25			
10/ 2/37	2:1 A-V block	0.205	0.53	1.28			
11/ 3/37	Incomplete A-V block with interference-dissociation	0.22–0.26	1.58	1.53	0.15	0.45	0.47

almost identical with the ventricular complexes at the time of 2:1 response (Fig. 1, *B*). Ventriculophasic sinus arrhythmia is present. Ventriculoauricular responses are of rare occurrence, and are spotted most easily when the longest P-R intervals are examined closely. Although P-P′ does not exceed the lower limits of normal interauricular periods (P-P) as measured in the whole curve, it is shorter than the average P-P. P′ is inverted in the two middle tracings, but not in the upper and lower.

Table I gives a summary of our observations in this case.

CASE 2.—A man, 76 years old, showed signs of congestive heart failure in February, 1937, with slight anginal pain on effort. There were never any fainting spells. Prostatectomy without complications was done at the age of 70 years; glycosuria had been found at the age of 69 years. When first seen by one of us (M. W.) on Aug. 25, 1937, his blood pressure was 220/80, and his pulse rate, 48. There were left ventricular enlargement, severe congestive failure, and a periodic type of breathing without distinct periods of apnea. Digalen was administered daily, in a dose corresponding to 0.2 Gm. of the powdered leaves, from August 29 until August 31, and in a dose corresponding to 0.15 Gm., from September 1 until September 10. Two injections of a mercurial diuretic (novurit) were also given. The edema subsided considerably, and the general condition improved markedly up to September 11, when he developed frequent "attacks," with loss of consciousness; once he injured himself by falling, but had no convulsions. When digalen was discontinued, his attacks stopped immediately, but the patient was in a state of confusion for several days and complained of severe headache on subsequent days. Nothing of note was observed later; the patient's compensation was maintained by means of 0.05 to 0.1 Gm. of powdered digitalis leaf, daily, and occasional intravenous administrations of novurit. He died from cerebral hemorrhage in July, 1938. Permission for a post-mortem examination was not obtained.

Electrocardiograms (seventeen records on twelve nonconsecutive days within six months).—

A. Aug. 25, 1937. The record shows complete A-V block with idioventricular rhythm. The auricular rate is 66, without marked arrhythmia. The ventricular action is regular at a rate of 47 to 50 per minute. QRS measures 0.12 second. The auricular rhythm, which is controlled by the sinus node, is disturbed at times by premature auricular complexes (P′) similar to those in Case 1. These premature P waves in Lead I differ from the normal P wave, in that they are slightly notched, and are inverted in Leads II and III. The premature P waves follow an idioventricular beat at an interval of 0.13 to 0.15 second and occur only at a P-P′ distance of 0.77 second or more (after a P-R of 0.62 second or more), while the normal P-P interval is about 0.91 second. The subsequent P′-P is lengthened without, however, fully compensating for the preceding shortening. Considering the abnormal P′ as retrograde P waves, the noncompensatory pause indicates that the retrograde impulse reaches the sinus node and disturbs its rhythmic impulse formation.

B. A record taken three days later shows essentially the same features.

C. Aug. 31, 1937 (Fig. 2, *A*, *B*, and *C*), third day of digitalis treatment. Here we have complete A-V block, with a few retrograde beats at P-P′ intervals of 0.75 second and more. R-P′ varies from 0.11 to

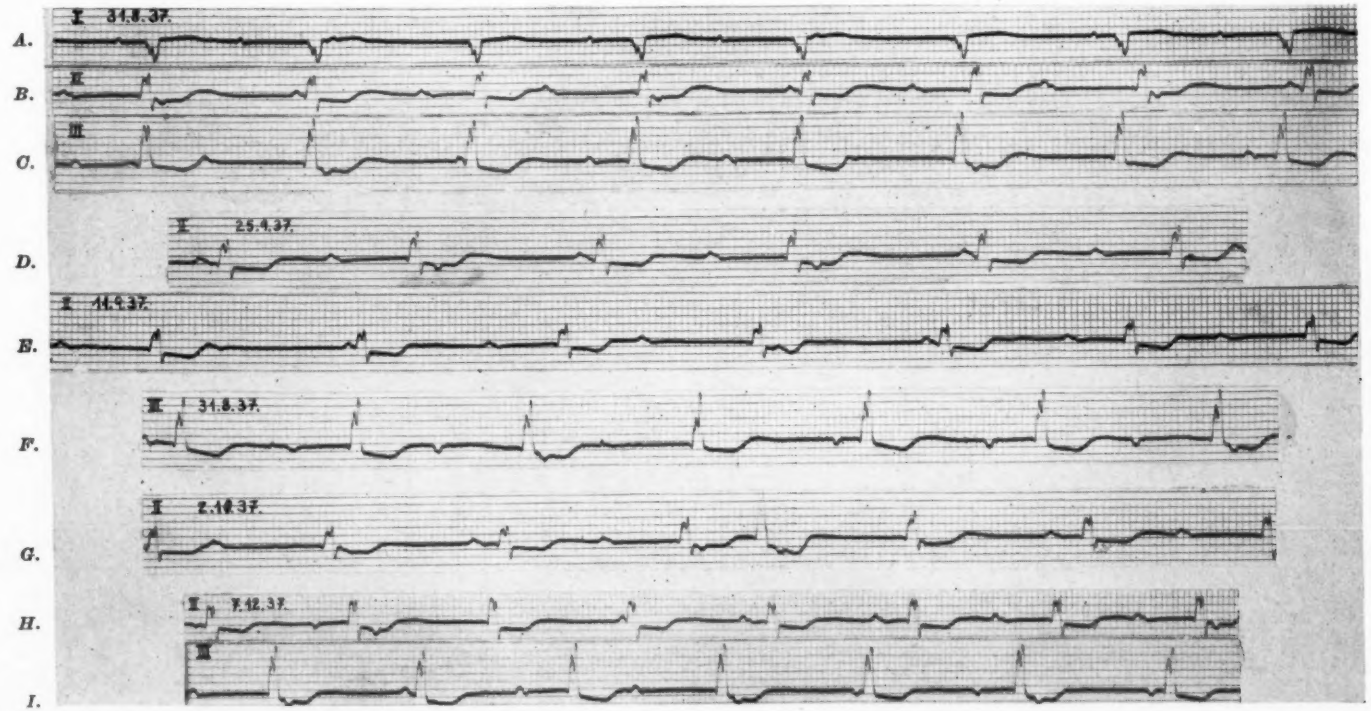

Fig. 2.—Case 2. Complete A-V block.

A to *C*, Retrograde conduction evidenced by the third and seventh P in Lead I, the second, sixth, and tenth P in Lead II, and the third and eighth P in Lead III. Note the upright P of retrograde conduction in Lead I.

D, Effect of digitalis. Retrograde conduction time (R-P'), previously 0.11-0.17 second, now measures 0.18 to 0.22 second. The absolute refractory period for retrograde conduction is also longer than before digitalization. Its duration is indicated by the second idioventricular beat with a P-R of 0.60 second, followed by retrograde conduction, and the sixth idioventricular beat with a P-R of 0.57 second, followed by retrograde block.

E, On the verge of digitalis poisoning. Complete retrograde block; otherwise, the first and last QRS should be followed by a retrograde P because of their long P-R distance.

F, Carotid sinus pressure produces slowing of the auricles, with inverted P waves throughout; these most likely represent the escape of an A-V nodal rhythm with orthograde block. The third and last QRS are followed by a premature P because of retrograde conduction of the idioventricular impulse.

G, An idioventricular beat with retrograde conduction is followed by a ventricular premature systole with retrograde conduction. The two retrograde P waves (P') in succession occur at an interauricular period (P'-P') which is shorter than the shortest period (P-P') between a retrograde P and a preceding normal sinus P. The retrograde conduction time (R-P') of the ventricular extrasystole is longer than the preceding R-P'.

H and *I*, Sinus arrhythmia with shifting of the pacemaker to the A-V node is responsible for the variations of P-wave contour. Retrograde conduction after inverted P waves occurs after shorter P-R distances than retrograde conduction after upright P waves; compare the second QRS in *H* and the sixth in *I* (both with short P-R followed by retrograde conduction) with the seventh in *H* and the third in *I* (both with long P-R followed by retrograde block). For explanation see text and diagram of Fig. 6.

Time intervals = 0.05 second.

0.17 second, in inverse proportion to the length of the preceding P-R. Fusion of an orthograde and late retrograde P is probable from the time relations, but is not reflected in the shape of the resulting P wave. Independent of retrograde conduction, there is a marked auricular arrhythmia with wandering of the pacemaker. The P waves are sometimes inverted, and show the same contour as the retrograde P waves (P′), but the time of their occurrence proves their independent origin. They are most likely retrograde responses to escapes of the A-V node which are blocked in the orthograde direction. These escapes occur mostly with a slowing of the auricles, such as follows retrograde conduction or is produced by carotid sinus pressure.

D. Sept. 11, 1937 (Fig. 2, *E*), at the time of digitalis intoxication. Here there are complete A-V and complete V-A block. The whole record, containing seventy-four ventricular cycles with every possible position of P, fails to show any sign of retrograde conductivity. The auricular action is very irregular, and multiple auricular escapes and extrasystoles are present. The idioventricular rhythm has also become irregular, and its rate ranges from 22 to 53. The disturbance of the idioventricular rhythm may explain the Adams-Stokes attacks which occurred on this day. Digitalis is also responsible for the alterations in the form of the ventricular complex.

E. Sept. 21, 1937, ten days after digitalis was discontinued. There is regular sinus action, with a rate of 63. There is no retrograde conduction. Several ventricular extrasystoles are present, interrupting the idioventricular rhythm.

F. Sept. 25, 1937 (Fig. 2, *D*). Here retrograde conduction has reappeared. It occurs only at a P-P′ of 0.82 second or more, and the transmission time (R-P′) is lengthened to 0.18 to 0.22 second. Thus, the absolute, as well as the relative, refractory period of retrograde conduction is affected by the accumulation of digitalis. Ventricular extrasystoles sometimes occur by chance after a retrograde P′, thus suggesting a "sandwiching," i.e., conduction from the ventricles to the auricles and back again to the ventricles. It can be easily shown, however, that such reciprocal rhythm does not occur in our case.

G. Oct. 2, 1937. Retrograde conduction occurs and the effect on it of digitalis administration has disappeared. In addition, there are numerous auricular extrasystoles with aberrant, upright P waves, auricular escapes with inverted P waves, and ventricular extrasystoles, some of them with retrograde conduction. This record and similar ones taken on other days made it possible to ascertain and compare the conditions for retrograde conduction after different types of auricular beats. It was found that retrograde conduction following inverted P waves occurred after shorter P′-R intervals than retrograde conduction following upright P waves, whatever the origin of the inverted P wave. The retrograde conduction time (R-P′) also tended to be shorter after retrograde auricular excitations.

Table II gives the data on one of several records taken on different days.

No significant features were added by later records. It was seen that, whenever an inverted P was due to supraventricular escape, it was followed by an idioventricular beat with retrograde conduction (Fig. 2, *H* and *I*), and, whenever two ventricular beats with retrograde conduction occurred in succession (Fig. 2, *G*), the second P′ of the pair occurred unusually early.

Thirty-five hundredths milligrams of strophanthin K, injected intravenously, failed to affect the rhythm. Barium chloride in doses of

TABLE II

REFRACTORY PERIOD FOR RETROGRADE CONDUCTION AFTER +P (SINUS P AND AURICULAR EXTRASYSTOLE) AND –P (RETROGRADE P AND ESCAPE) IN CASE 2*

		NO RETROGRADE CONDUCTION	RETROGRADE CONDUCTION WITH R-P′ 0.205-0.16	RETROGRADE CONDUCTION WITH R-P′ 0.15-0.135
P-R in 1/100 sec.	after +P	29, 30, 36, 58	56.5, 58, 88, 88	
	after –P	18, 19, 22, 28	28, 28, 33, 33.5, 36, 40 42, 42, 42.5, 43, 43.5, 48, 48	51.5, 54, 54.5, 56, 58

*For discussion see text.

TABLE III

VARIATIONS IN RETROGRADE CONDUCTION IN CASE 2

NUMBER OF RECORD	DATE	RATE		LONGEST P-R NOT FOLLOWED BY RETROGRADE CONDUCTION PLUS SHORTEST R-P′ (1)	SHORTEST P-P′	R-P′	NOTE
		AUR.	VENT.				
1	8/25/37	66	48	0.63	0.77	0.13-0.15	(1) To show upper limit of blocked retrograde conduction (2) Digitalis from 8/29/37 to 9/10/37 (3) Ventricular extrasystoles (4) Auricular extrasystoles
2, 3	8/28/37	55	41	0.54	0.64	0.13-0.17	
4	8/31/37(2)	62	48	0.67	0.75	0.11-0.17	
5, 6	9/11/37(2)	54	22-53 (2)	>0.83			
7	9/21/37	63	41-45	>0.98			
8-10	9/25/37	59	41	0.75	0.82	0.18-0.22	
11	10/ 2/37	60	33-44 (3)	0.71	0.73	0.13-0.16	
12	10/26/37	58	43	0.72	0.75	0.15-0.17	
13	11/ 2/37	50-92 (4)	41-48	0.67	0.71	0.14-0.16	
14	12/ 7/37	58	45	0.61	0.72	0.11-0.18	
15, 16	2/ 7/38	57	40	0.60	0.70	0.15-0.20	
17	2/25/38	58	46	0.67	0.87	0.14-0.19	

0.03 to 0.09 Gm. daily, during three weeks, increased the auricular and ventricular arrhythmia, but was without effect on conduction or on the symptoms.

Table III shows the variations of retrograde conduction over the whole period of observation.

CASE 3.†—The patient was a man, 48 years of age. Bradycardia had been observed since 1936. At this time he complained of mild attacks of anginal pain. The blood pressure was 150/80; the blood Wassermann reaction was negative. Roentgenologic examination showed marked sclerosis of the aorta. Adams-Stokes attacks developed, and became more frequent as time went on. The patient succumbed to one of these attacks in August, 1938.

Electrocardiograms (four records of Lead II only, taken on four nonconsecutive days within seven weeks).—

A. Nov. 6, 1937 (Fig. 3, *A*). Complete A-V block alternates with 1:1 A-V response, probably partly because of the slight change in auricular rate. The sinus rate varies from 40 to 54 per minute as a result of

†We are indebted to Dr. Leo Hahn, Birmingham, England, formerly of Teplitz-Schoenau, Bohemia, for permission to use this case.

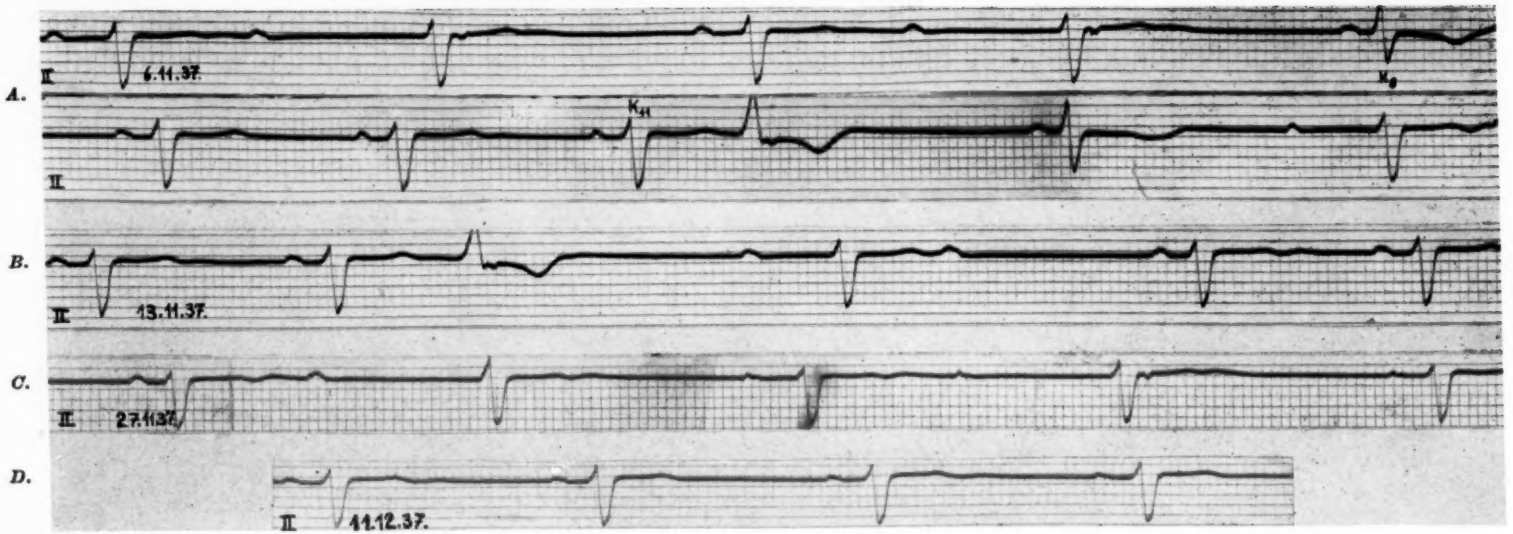

Fig. 3.—Case 3. (Courtesy of Dr. L. Hahn.)

Incomplete and unstable A–V block with retrograde conduction after both idioventricular beats and ventricular extrasystoles. The retrograde conduction time is shorter than the orthograde conduction time. For full discussion see text.

Time intervals = 0.05 second.

ventriculophasic sinus arrhythmia. The ventricular action is regular at 32 per minute, and QRS measures 0.14 second. Idioventricular and conducted beats do not differ in contour. The P-R interval, when conduction occurs, varies from 0.17 to 0.185 second. The second and fourth idioventricular beats (typical of others not shown) show retrograde conduction, producing an inverted P′, 0.15 second from the preceding R. This occurred whenever P preceded an idioventricular beat by 0.51 to 0.80 second. The P′ of retrograde conduction is not always premature, but it is invariably followed by a lengthened P′-P interval. The only ventricular extrasystole seen on this day (second strip) is followed by retrograde conduction, with a R-P′ interval of 0.15 second. The fifth ventricular complex (top line) and the first postextrasystolic complex show some difference in the shape of QRS and T. The time of their occurrence makes it likely that they result from fusion of idioventricular and conducted impulses. However, it is unlikely that fusion of impulses, both of which produce the same type of QRST, should result in an aberrant type unless improved conduction occurred after an exceptionally long ventricular pause and resulted in the ventricular complex aberration.

B. Nov. 13, 1937 (Fig. 3, *B*). Here we have 1:1 A-V response, interrupted on five occasions by ventricular extrasystoles. Each of these is followed by the premature P waves which represent retrograde conduction. The subsequent sinus P is blocked, and the ventricle escapes for one or two beats, until an auricular impulse occurs at a suitable interval after the end of the refractory period, when it is transmitted to the ventricle and 1:1 A-V conduction is resumed. The orthograde conduction time measures 0.18 to 0.20 second; and the retrograde conduction time, 0.15 second. The refractory period for orthograde conduction, with the exception of postextrasystolic block, ends at 0.57 to 0.62 second after idioventricular beats; retrograde conduction is confined to P-P′ intervals of 0.63 to 1.06 seconds.

C. Nov. 27, 1937 (Fig. 3, *C*). There is complete A-V block with ventricular complexes of the same type as before. The auricles are under the control of three foci: the sinoauricular node, the ventricular pacemaker (retrograde conduction), and a slow ectopic auricular focus with upright P waves. The retrograde conduction time measures 0.160 to 0.175 second, dependent upon the preceding P-R, and the pause after retrograde P waves is fully compensatory.

D. Dec. 11, 1937 (Fig. 3, *D*). There is normal A-V succession, and the auricles are stimulated by the ectopic center that was present on November 27. The auricular rate is 36 to 39, and P-R is 0.195 second.

SUMMARY OF OBSERVATIONS IN CASES REPORTED

Our three cases, as well as the nineteen cases found in the literature (all listed in Table IV) and the three additional cases (illustrated in Figs. 4 and 5, clinical data in Table IV), present certain identical features.

1. Inverted P waves occur at short intervals after idioventricular beats in cases of A-V block. These P waves, which we consider to be due to backward conduction of ventricular impulses to the auricles, are always inverted in Leads II and III; in Lead I, however, P′, as a rule, is either upright, diphasic, or isoelectric. It is upright in CF_2 and inverted in Lead IVR in the few cases in which these leads were recorded.

That the P′ of retrograde conduction is not the mirror image of the orthograde P was true also in nodal extrasystoles, in A-V nodal escapes, and in paroxysmal tachycardia of A-V nodal origin. This peculiar pattern of the retrograde P wave was found in the illustrations of such arrhythmias in various textbooks and monographs, as well as in ten out of twelve of our own recent cases. Attention has been drawn to it by Daniélopolu and Danulesco[3] and Wenckebach and Winterberg.[4]

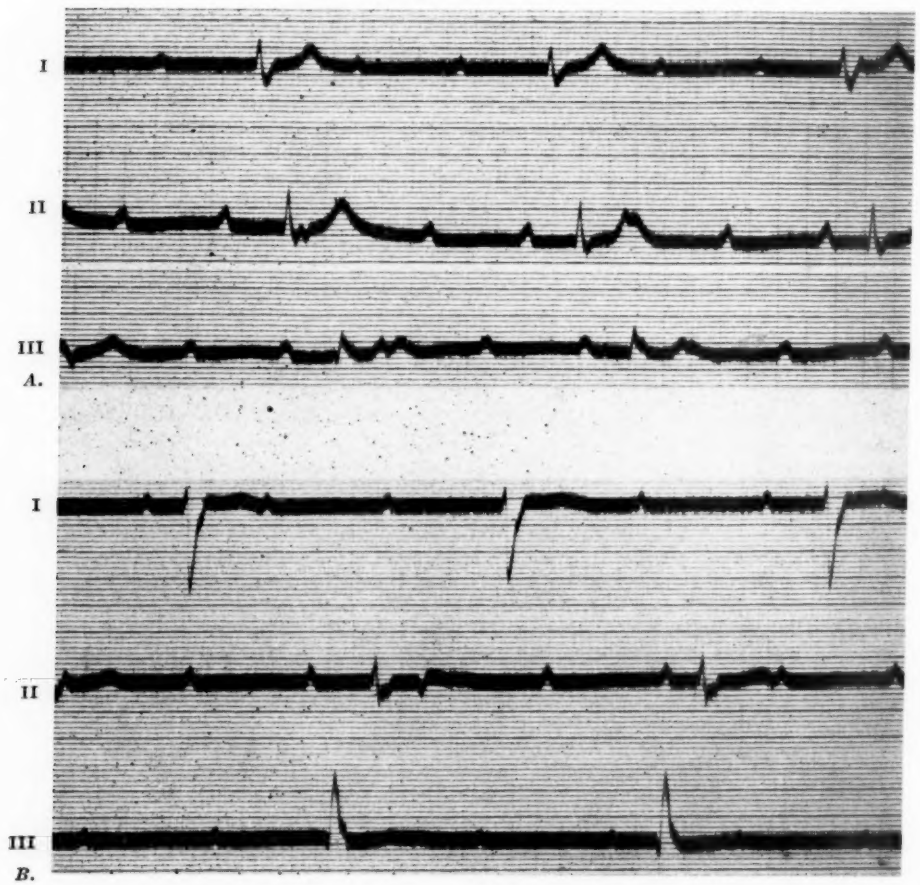

Fig. 4 (Courtesy of Dr. J. Parkinson).—Two cases of complete A-V block with retrograde responses of the auricles.

(*A*) The third P in Lead II, the first P in Lead III, and (*B*) the seventh P in Lead I (?), and the fourth P in Lead II are due to retrograde conduction. Note the marked prolongation of the retrograde conduction time (0.38 second) in case (*B*). The auricular pause after the retrograde P waves is fully compensatory, indicating that the retrograde impulse does not reach the S–A node.

Time intervals = 0.04 second.

2. In the majority of the cases the A-V block is of arteriosclerotic origin, and organic disease of the bundle of His is apparently the underlying condition. In only one case out of twenty (Table IV) was the patient under 48 years of age, and this case does not strictly belong in

the group because it is one of reciprocal rhythm. No case was encountered of congenital heart block, of A-V block due to myocarditis, or of A-V block following digitalis medication.

3. Unstable or incomplete A-V block, instead of complete block, occurred in more than half of our cases (Table IV). This seems to exceed the incidence of incomplete block in clinical heart block as a whole. It should be realized that the absence of conducted beats in a record does not necessarily prove that the conducting system is completely unable to transmit impulses. Partial A-V block with a long refractory period of the junctional tissue and a relatively rapid, passive, nodal or idioventricular rhythm can easily imitate complete A-V block. Theoretically, we are unable to rule out the possibility in any case of so-called complete A-V heart block that only partial A-V block exists, with complete A-V dissociation due to escape of the lower rhythm center.

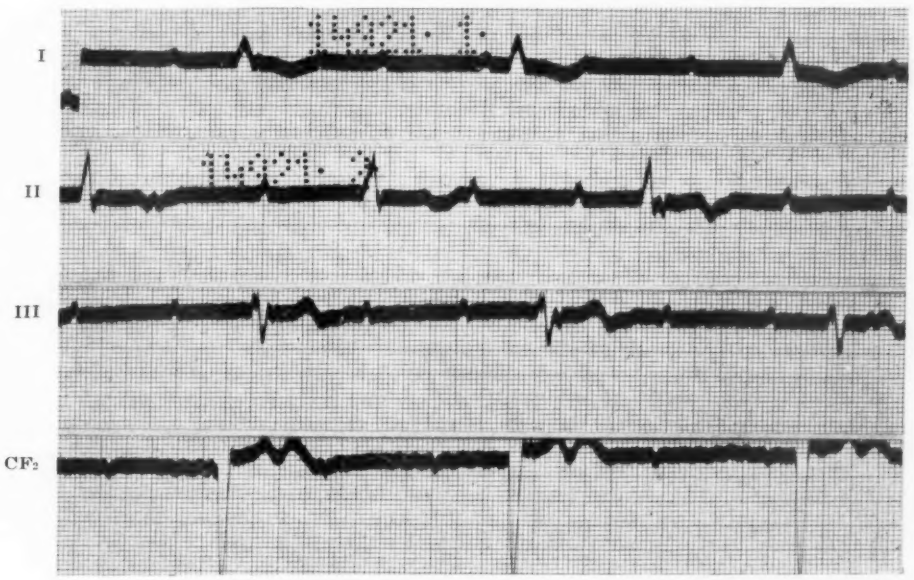

Fig. 5 (Courtesy of Dr. L. N. Katz).—Complete A-V block with retrograde response.

The third P in Lead I, the sixth P in Leads II and III, and the fifth P in Lead CF_2 represent retrograde P waves. The third P in Lead III, which is intermediate in contour between the sinus P and the retrograde P, is a fusion beat; it is only slightly premature, and is due to simultaneous invasion of the auricles by the orthograde impulse from above and by the retrograde impulse from below. Note the "ventriculophasic sinus arrhythmia of heart block"; a P–P interval which contains a ventricular complex is shorter than a P-P interval which does not.

Time intervals = 0.04 second.

4. When incomplete block was present, retrograde conduction was confined to idioventricular impulses; the only exception was in a somewhat different case (Case 2 of Wolferth and McMillan[5]), in which reciprocal beats occurred in an instance of 2:1 A-V block.

5. Idioventricular rhythm arising below the bifurcation of the common bundle was present in all but five cases. However, it is possible that, in

TABLE IV

THE MAIN OBSERVATIONS IN ALL PUBLISHED CASES OF AURICULOVENTRICULAR BLOCK WITH VENTRICULOAURICULAR RESPONSE

NUMBER	AUTHOR	YEAR OF PUBLICATION	AGE	SEX	B.P. (SYSTOLIC)	WASSERMANN REACTION	VENTRICULAR RATE	AURICULAR RATE	ORIGIN (TYPE) OF IDIOVENTRICULAR RHYTHM	STABILITY OF BLOCK	DEGREE OF BLOCK	ORTHOGRADE P-R	RETROGRADE R-P'*	DIRECTION OF P_1'*	SHORTEST P-P'*	COMPENSATORY PAUSE	AURICULAR FUSION BEATS
1	Cohn and Fraser[7]	1913	62	M		? +	43	75	idiov.	unstable	2:1 and complete	0.20	0.10-0.14	?	0.64	+ ?	–
2	Wilson and Robinson, II[8]	1918		M		–	36-40	75-103	idiov., variable	stable	complete		0.20-0.34	?	0.58		
3	Daniélopolu and Danulesco[3]	1919	57	M		+	25	88	idiov., variable	stable	complete		0.16-0.22	+	0.66	+	+
4	Veil and Codina-Altès, I[8]†	1923							idiov.	unstable	incomplete	0.20		?	0.57		
5	Veil and Codina-Altès, I[9]†	1923							idiov.	stable	complete			?			
6	Barker[10]	1926	51	M	170	–	34-42	62-77	idiov., variable	unstable	1:1 to complete	0.20	0.23-0.24	?	0.69	+	+
7	Wolferth and McMillan, I[5]	1929	60	M			28	50	suprav.	stable	complete		0.16	–	0.64-0.79‡	–	–
8	Wolferth and McMillan, II[5]	1929	37	F			29-37	56-78	idiov.	?	2:1	0.41-0.64	0.22-0.26	+	0.72	+	+
9	Wolferth and McMillan, III[5]	1929	48	F	135	–	31	90	suprav.	unstable	1:1, 2:1, complete	0.15	0.16	?	0.60-0.68‡	+	–
10	Levine[11]	1936					27	66	idiov.	?	complete		0.15	?	0.70	+	?
11	Schramm and Korth[12]	1937	52	M			27	65	suprav.	unstable	complete and incomplete	0.36	0.17-0.34	–	0.70	–	+
12	Lequime and Sanabria[13]	1937	73	M	260	–	37	94	suprav.	stable	complete		0.18-0.19	+	0.55	+ ?	+

13	Dubbs[14]	1938	72	M	160	–	24	75	idiov.?	unstable	1:1 and complete	0.24-0.32	0.13	?	0.66	+	–
14	Kline et al.[6]	1939	68	F	200		28-37	65-88	idiov., variable	unstable	1:1 and complete		0.12-0.14‡	+	0.48	+	–
15	Froment et al.[15]	1939	57	M	140	–	33	72-93	idiov.	unstable	incomplete	0.16-0.18	0.20	?	0.52	+	
16	Graybiel and White[16]	1941	82	M			33	84	idiov.	stable	complete		0.15	–	0.68	+	+
17	Bain, I[17]	1941	67	M	190	–	26	75	idiov., variable	stable	complete		0.16-0.18	?	0.68	+	
18	Bain, II[17]	1941	67	M	200	–	27-37	71-88	idiov., variable	unstable	2:1, complete	0.22-0.26	0.16	?	0.58	–	
19	Kisch and Zucker[18]	1942	64	M	120	–	24-41	60-91	idiov.	stable	complete		0.14-0.20	?	0.60	+	
20	Katz[2]	1941, 1943	50	M	150		26-29	70-75	idiov.	stable	complete		0.15-0.17	+	0.63	+	+
21	Parkinson, I	1941					27	79	idiov.	?	complete		0.13-0.15	?	0.60	+	–
22	Parkinson, II	1941					25	67	idiov.	?	complete		0.38	?	0.84	+	–
23	Winternitz and Langendorf, I	1941	62	F	200	–	27-37	73-92	idiov. and suprav.	unstable	2:1, incomplete, complete	0.205-0.26	0.15	+	0.57-0.62	+	+
24	Winternitz and Langendorf, II	1941	76	M	220		22-53	48-85	idiov.	stable	complete		0.11-0.22	+	0.64-0.87‡	–	+
25	Winternitz, and Langendorf, III	1941	48	M	150	–	29-32	40-59	suprav.	unstable	1:1 and complete	0.17-0.20	0.15-0.17	?	0.85	+	–

*P′ = P due to retrograde response.

†The cases published in 1923 are obviously those mentioned in the monograph in 1928, and are quoted only once.

‡On different days.

some of them, intraventricular block was present in addition to A-V block, in which event a rhythm originating above the bifurcation of the bundle would imitate a tertiary origin.

6. Retrograde conduction time ranges from 0.10 to 0.23 second, and was less than 0.18 second in nineteen out of the twenty-five cases. With the shortest P-P′ it may be prolonged to 0.38 second. Thus, in the majority of cases, V-A conduction is well within normal limits as compared with normal A-V conduction. In most cases of incomplete A-V block, retrograde conduction takes place more readily than orthograde conduction, as evidenced by a considerably shorter R-P′ than P-R in these cases. However, it should be realized that the relative speed of orthograde and retrograde conduction is not always indicated by the relative length of P-R and R-P′, for these two intervals do not measure the time required by the impulse to cover the same distance. This is particularly true when the ventricular pacemaker is in the A-V node.

7. The occurrence of retrograde conduction and the duration of R-P′ depend on the preceding P-R distance. The shortest P-R (0.32 second) which permitted subsequent retrograde conduction was observed in the case of Kline, Conn, and Rosenbaum.[6] Thus, the manifestation of retrograde conductivity in A-V block requires that the auricular rate be not too rapid. The sum of the shortest P-R (0.32 second) and the average R-P′ (0.18 second) gives a duration of 0.50 second, corresponding to a rate of 120/minute as about the shortest P-P distance (fastest auricular rate) that will permit a retrograde P wave. With a P-P distance of 0.49 second or less, the normal orthograde impulse will preclude the occurrence of an auricular response to a retrograde impulse.

Table IV shows the main observations in all published cases. It includes a case of Dubbs,[14] which we believe represents another instance of retrograde conduction, although the author does not comment upon this, one of Lequime and Sanabria,[13] described by them as an instance of complete block with independent auricular and ventricular rhythm, and one of Levine.[11]

RETROGRADE CONDUCTION IN A-V BLOCK

The obvious relationship between retrograde conduction and the preceding auricular pause has been considered by several authors (Daniélopolu and Danulesco[3] and others) as a manifestation of the refractory period of the auricles. However, no evidence has been presented for this assumption. The refractory period of the auricles is known to be short, and there is no evidence of intra-auricular block in the majority of such cases. Furthermore, in our second case, some auricular extrasystoles occurred after much shorter P-P intervals than those which seem to prevent retrograde conduction. The sinoauricular impulses not only stimulate the auricles, but travel down through the A-V node and the bundle of His until they reach the depressed region, which they fail to pass. Our second case demonstrates clearly that it is the state of the junctional region of depression or block, and not of the auricle, which

determines whether retrograde transmission will occur or fail. As pointed out before, the earliest retrograde response which occurred after an upright P (due to a normal or extrasystolic auricular impulse with positive P) was preceded by a definitely longer P-R than that of the earliest retrograde response which came after an inverted P (due to a retrograde response or supraventricular escape). This observation, which is inexplicable on the basis of the refractory period of the auricle, can be readily explained by the mechanism indicated in the diagram of Fig. 6.

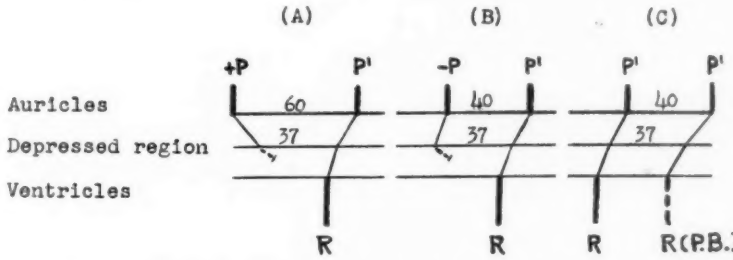

Fig. 6.—Case 2. Diagram to illustrate the relation between the recovery period for retrograde conduction and the manifest interauricular period. Time in 1/100 second.

Retrograde conduction after (*A*) orthograde P (+P), (*B*) P of a supraventricular escape (–P), (*C*) P of retrograde conduction (P').

The earliest possible retrograde conduction after an upright P occurs at a P–P' which is much longer than the P'–P' of the earliest retrograde conduction after an inverted P. P–P' includes the additional time required both by the impulse from above to reach the depressed region and by the impulse from below to travel from the depressed region to the auricle.

Two conclusions are warranted from this analysis: first, that the actual refractory period in all cases is shorter than indicated by the shortest P-P' interval, the difference ranging from 0.2 to 0.3 second, as can be seen from Table II; and, second, that the orthograde and retrograde impulses must travel for a certain distance along the same pathway.

The paradox of normal retrograde response in cases of high-grade auriculoventricular block has puzzled all observers, and various theories have been advanced to explain it. Cohn and Fraser[7] hesitated to assume that the premature, inverted P waves were due to conduction in a reverse direction. The explanation they put forward was that the auricles were mechanically stimulated by the ventricular action. Wilson and Robinson,[8] in 1918, believed that the ventricular beats promote the discharge of auricular extrasystoles, and compared this phenomenon with the peculiar ventriculophasic sinus arrhythmia in A-V block. Later investigators discarded the mechanical theory, which is also considered unsatisfactory by Parkinson[19] and Katz.[2] In fact, it fails to explain some of the principal features of the arrhythmia, e.g., the close relation between the preceding auricular pause and the following R-P'. The analogy to the sinus arrhythmia of A-V block does not seem to be close, for the latter is of common occurrence, whereas inverted P waves are exceptionally rare, if found at all, in partial block without escaped beats. Furthermore, in several cases of the group of A-V block with V-A response, a ventriculophasic sinus arrhythmia was not present.

Barker,[10] on the basis of animal experiments[20] in which a sudden increase in intraventricular pressure was found to cause a premature beat, assumed that ventricular contraction mechanically stimulates some focus in the bundle above the supposed lesion, provoking a premature beat which is then conducted to the auricles by the normal path. The chief objection to Barker's theory, previously also raised by Wolferth and McMillan,[5] is that the interval R-P′, which measured only 0.10 second in a case of Cohn and Fraser and 0.11 second in our Case 2, is too short to cover Barker's double mechanism.

Daniélopolu and Danulesco[3] were the first to suggest retrograde conduction as an explanation for inverted P waves in A-V block. Since orthograde conduction was completely absent in their cases, they assumed that retrograde transmission took place by pathways other than the bundle of His. Scherf and Shookhoff[21] refer to animal experiments[22] which showed that, under certain circumstances, parts of the conduction system of the frog's heart may allow orthograde conduction, whereas, in other parts, only retrograde conduction is possible. Schramm and Korth[12] suggest the bundle of Kent as a possible pathway for retrograde conduction. Our evidence, we believe, is opposed to this theory, for both forward and retrograde impulses appear to use the same path (Fig. 6).

The heart in one of the cases of Wolferth and McMillan[5] was examined histologically, and destruction of about 7/8 of the diameter of the bundle of His was found. The authors concluded from the localization and conical shape of the lesion that the orthograde impulse had to travel through a slightly damaged area before reaching the major obstacle. Thus, the weakened impulse was unable to overcome the latter, whereas the retrograde impulse traveled first through the major lesion in an unattenuated condition and then passed the minor obstacle as well. This theory of unidirectional block, which is similar to Mines'[23] explanation of unidirectional block as due to asymmetrical decremental conduction in a depressed region, has found strong support in the experiments of Ashman and Hafkesbring,[24] who succeeded in producing unidirectional block by asymmetrical compression of a tortoise heart muscle strip. Rothberger[25] calls the explanation of Wolferth and McMillan[5] credible, but hypothetical.

A thorough histologic examination of the conduction system was also reported in the case of Lequime and Sanabria.[13] Like Wolferth and McMillan,[5] the authors found the lesion near the bifurcation of the bundle. In addition, there was complete interruption of both bundle branches which may have occurred after the electrocardiogram was taken.

An autopsy was performed in the case illustrated in our Fig. 5, by Dr. Maurice Lev and Dr. Otto Saphir at the Michael Reese Hospital (Chicago), and we are indebted to them for permission to publish the report of the post-mortem examination.

The heart weighed 375 grams. The epicardium and endocardium were smooth and glistening. The endocardium covering the basilar portion of the left ventricular aspect of the muscular ventricular septum was dis-

tinctly depressed and grayish white in color. The valvular apparatus presented no abnormality. The myocardium of the left ventricle measured 1.1 cm. in thickness. On section it was grayish red, with many irregular, grayish-white streaks. The myocardium of the muscular ventricular septum beneath the membranous portion, on section, presented an irregular, whitish-gray, depressed area, measuring 2.5 cm. in greatest dimension. This extended throughout the whole thickness of the septum in this region. The myocardium of the right ventricle measured 0.2 to 0.3 cm. at the pulmonic orifice, 0.2 to 0.3 cm. at the tricuspid orifice, and 0 to 0.1 cm. at the left lateral margin. Both the right and left ventricular chambers were dilated. The lining of the coronary arteries presented moderate sclerosis, but the lumina were not encroached upon. The aorta also showed moderate sclerosis.

Histologic examination of the myocardium revealed a mild and, in areas, moderate, diffuse increase in young connective tissue cells. The myocardial fibers showed no remarkable changes. The small arteries showed some intimal thickening. The subepicardial fat involved the myocardium of the right ventricle.

Serial sections through the base of the muscular ventricular septum revealed the following: The A-V node and all but the most distal part of the common bundle showed no changes. At the point of giving off of the left bundle branch, the fibers were apparently interrupted by a large amount of connective tissue. This connective tissue had replaced much of the myocardium of the base of the muscular ventricular septum, and corresponded to the white area noted grossly. This connective tissue extended to the endocardium of both the right and left ventricles, and numerous connective tissue interruptions were obvious in the upper part of the right and left branch of the bundle. The fibers of these branches that remained were markedly eosinophilic and granular. The arteries showed slight intimal thickening.

The cardiac diagnosis was: (1) Localized area of fibrosis of the myocardium of the base of the muscular ventricular septum, with involvement of the distal portion of the bundle of His and both bundle branches; (2) moderate fibrosis of the myocardium elsewhere; (3) moderate coronary sclerosis; and (4) hypertrophy and dilatation of the right and left ventricles.

The abnormalities in this case are not unlike those of Wolferth and McMillan, and a similar explanation could be applied. However, the data are still not complete enough to assume that this is the mechanism. Retrograde conduction in A-V block may be more frequent than we assume, for retrograde conductivity cannot be excluded just because no premature, inverted P waves are recorded in short strips or because single observations are made in a case of A-V block. It seems significant that several observers, once their attention was drawn to the phenomenon of retrograde conduction in A-V block, were able to find other examples in their material. It is our impression that, on sufficiently close observation, a large proportion of cases of incomplete and unstable A-V block of arteriosclerotic origin will display unimpaired retrograde conduction.

Schramm and Korth[12] raise the possibility that different impulse strength might account for differences in orthograde and retrograde conduction. However, the quality of the impulse does not seem to play a decisive role, for ventricular extrasystoles are conducted to the

auricles with the same ease as idioventricular impulses of tertiary or A-V nodal origin[3, 5, 9] (and our Cases 2 and 3). On the other hand, auricular extrasystoles and supraventricular escapes are blocked out in the same way as are sinus impulses (our Case 2).

Kline, Conn, and Rosenbaum[6] made an ingenious attempt to explain the phenomenon by assuming a supernormal recovery phase, as first described in cases of incomplete A-V block by Lewis and Master.[26] Kline, et al., assumed that stimulation of the auricle promoted a supernormal phase of conduction in either direction. This explanation will not account for our Case 2. Here, with arrhythmic auricular action, orthograde impulses may be blocked in early auricular diastole, whereas retrograde impulses may be transmitted in late auricular diastole.* Kisch and Zucker[18] point out that the recovery curve constructed in their case is not of the type expected with a supernormal phase. Like Kline, et al., Froment, Masson, and Gonin[15] published a case of supernormal recovery phase, together with another case of retrograde response in A-V block; but these authors do not comment upon the possibility of a supernormal recovery phase phenomenon in the latter case.

In summary, neither the mechanical or extrasystolic hypothesis, nor the hypothesis of different pathways for orthograde and retrograde conduction, nor the assumption of a supernormal recovery phase is able to explain the facts in a satisfactory way. We are led to the conclusion that the same fibers of the specialized muscular tissue which are unable to conduct orthograde impulses are able, at the same time, to conduct in reverse direction.

This condition, although puzzling, is not without analogy in the pathology of human arrhythmias. Typical examples of A-V dissociation with interference (Mobitz's "Interferenz-dissoziation") are due to a higher rhythmicity of the A-V node, and A-V conduction is otherwise undisturbed. The laws of interference-dissociation can be applied to the arrhythmia of A-V block with V-A conduction, if the direction of conductivity is reversed. The analogy of the two conditions is shown in Table V. Thus, the arrhythmia under discussion may be called *interference-dissociation between ventricle and auricle.*

Mobitz[27] explained the retrograde block in his cases by a lack of excitability of the auricles in response to retrograde impulses, with V-A conduction, as such, unimpaired. A similar explanation could be put forward for A-V block with normal V-A conduction. With normal conductivity in either direction, a lack of response in the ventricles to normal orthograde impulses would have to be assumed. Although we feel that the analogy between Mobitz's arrhythmia and that which we are dealing with is not merely accidental, we cannot accept his explanation, which has already been criticized by Scherf and Shookhoff[21] and Scherf,[28] among others.

*On one occasion an idioventricular beat which gave rise to a retrograde P occurred more than 1.0 second after the retrograde P of a preceding ventricular extrasystole. The same record showed retrograde conduction after a P'-R of only 0.28 second.

TABLE V

	INTERFERENCE-DISSOCIATION (MOBITZ)	A-V BLOCK WITH PRESERVED V-A RESPONSE
Auricular rate	Slower than ventricular rate	Faster than ventricular rate
A-V conduction	Normal, failing only after short R-P intervals	Grossly impaired or absent
V-A conduction	Absent	Normal, failing only after short P-R intervals
Conduction time	Normal or prolonged, dependent upon preceding R-P	Normal or prolonged, dependent upon preceding P-R
Type of "captures"	Ventricular	Auricular
Digitalis	May induce complete A-V block	May induce complete V-A block

Discussed in text.

We must content ourselves with the statement that orthograde and retrograde conductivity are different functions of the conducting system which may be impaired independently in the arrhythmia under discussion, as in other cases of ectopic impulse formation, both in man and experimental animals.

SUMMARY AND CONCLUSIONS

1. Three cases are described in which A-V block of various degree and stability occurred while conduction of ventricular impulses to the auricles was normal.

a. Case 1 showed unstable, occasionally complete, orthograde A-V block of arteriosclerotic origin. Retrograde conduction occurred in late auricular diastole only, and was followed by a compensatory pause. This proves that the retrograde impulses failed to reach the sinus node. Orthograde conduction, when present, was slower than retrograde conduction. Auricular fusion beats were present, resulting from simultaneous orthograde and late retrograde invasion of the auricles.

b. Case 2, observed over a long period of time, showed complete A-V block as a result of arteriosclerosis. Digitalis in average doses produced complete retrograde block, followed later, as the effect of the drug subsided, by a lengthened refractory period and a prolonged retrograde conduction time. The occurrence of ventricular extrasystoles and of A-V nodal escapes permitted a special study of the refractory period for retrograde conduction. Evidence is presented that retrograde conduction does not depend on the preceding auricular pause, but upon the recovery time of the depressed region within the A-V conducting system after the impulse invades it. The actual duration of the refractory period of this area is considerably shorter than the shortest interval (P-P′) between a normal P wave and a retrograde one: it equals the shortest P′-P′ of two retrograde responses in succession if they have the same R-P′. The variations of the refractory period over long intervals were inconsiderable. The retrograde impulse, in this case, reached the sinoauricular node, for no fully compensatory pause was present. Auricular fusion beats were present, as in Case 1.

c. Case 3 showed unstable, sometimes complete, A-V block, with normal retrograde response that was confined to ventricular impulses, as in Case 1. Intraventricular block was present in addition to A-V block. Orthograde conduction, when present, was slower than retrograde conduction. Ventricular extrasystoles were conducted to the auricles with the same ease and with the same R-P′ intervals as automatic ventricular beats of supraventricular origin. The pause after retrograde conduction was fully compensatory.

2. The electrocardiograms of two additional patients and that of one other patient, with autopsy report, are reproduced.

3. Nineteen cases of A-V block with V-A response from the literature, some of them hitherto unrecognized as cases of unidirectional block, are reviewed.

4. Retrograde excitation of the auricles gives a definite pattern of the retrograde P waves. The retrograde P is always inverted in Leads II and III, but may be upright or diphasic in Lead I; frank inversion in Lead I was not seen in our own nor in most of the published cases. Similarly, as a rule, the retrograde P in Lead I of extrasystoles or escaped beats is not inverted.

5. The different explanations which have been offered for the phenomenon of premature, inverted P waves in A-V block are reviewed. The assumption of an extrasystolic origin is rejected, as well as the thesis that A-V and V-A conduction pass along different pathways. Neither can a supernormal recovery phase be accepted as the explanation of the condition.

6. The phenomenon is regarded as a special, but by no means rare, type of incomplete heart block, and represents the reverse of Mobitz's interference-dissociation. Orthograde and retrograde conduction are considered as distinct functions of the special muscular tissue; they may be impaired separately or together, as shown by clinical observation and animal experiment.

7. The common feature in the three cases in which histologic examination of the conduction system was carried out is the absence of significant changes in the A-V node and upper part of the common bundle, whereas marked degenerative changes were present near the bifurcation of the common bundle, with involvement of the upper portions of one or both bundle branches. If this peculiar localization of the lesion is responsible for unidirectional block, the arrhythmia described may be of value in localizing the lesion of the A-V conduction system in cases of high-grade or complete A-V block.

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CARDIOVASCULAR DYNAMICS IN PATIENTS WITH ANGINA PECTORIS

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MOST physicians feel that the fundamental cause of angina pectoris is, largely or entirely, disease of the coronary arteries, and, accordingly, many studies have been made of the function of the coronary arteries and myocardium in patients with angina pectoris. There are, however, few physiologic data on the status of the circulation as a whole in this syndrome, and it was therefore considered desirable to record measurements of the general cardiovascular dynamics in patients with severe angina pectoris, uncomplicated by congestive failure, cardiac arrhythmia, or valvular disease.

MATERIAL AND METHODS

Twenty-two patients with a history of angina pectoris, but with no signs or symptoms of congestive failure, cardiac arrhythmia, or valvular disease, were studied. They ranged in age from 42 to 65 years; four (Cases 7, 10, 18, and 19) were less than 50 years of age, and three (Cases 16, 17, and 21) were more than 60 years old. Six (Cases 2, 3, 5, 8, 12, and 15) were women.

All measurements were made with the patient in the postabsorptive state, under basal conditions, after a rest of one-half to one hour; no attacks of angina occurred during any of the studies. Two different methods were employed in measuring the cardiac output: the acetylene method was used in Cases 1, 2, and 3, and the ethyl iodide method in Cases 4, 5, and 6. Studies by means of the acetylene method were made with the patient in a semirecumbent position; the basal metabolic rate was measured in duplicate first, utilizing a Collins-Benedict-Roth spirometer; calculations were made by means of the Aub-DuBois normal standards. The pulse rate was then counted twice, after which, two measurements of the arteriovenous oxygen difference were made according to the technique of Grollman, Friedman, Clark, and Harrison.[1] The minute volume output of the heart was calculated from the arteriovenous oxygen difference and the oxygen consumption; the latter was estimated from data obtained during the measurement of the basal metabolic rate. When measurements were made by means of the ethyl iodide method, the technique of Starr and Gamble[2] was used, and the oxygen consumption and basal metabolic rate were measured by the Tissot method simultaneously with the minute volume output of the heart; the patient was in a semirecumbent position. After the cardiac output was estimated by either method, the venous pressure was measured with the patient recumbent, using the method of Moritz and von Tabora,[3] after which the circulation time was measured with sodium dehydrocholate.[4] The vital

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capacity was then measured with a spirometer. Arterial pressure was estimated from time to time, using a mercury manometer with the standard cuff.

CASE REPORTS

CASE 1.—A 53-year-old retired storekeeper had a history of substernal squeezing pain beginning sixteen years previously. At first the pain occurred only occasionally, but its frequency increased, particularly in the preceding two years, so that, at the time of the present study, walking 100 yards regularly brought it on. It also occurred occasionally when the patient was at rest, and sometimes it awoke him from sleep. Initially the pain radiated to both arms, but, following myocardial infarction, ten months previous to this study, the radiation extended down the trunk to the legs and up into the jaws. The pain was often associated with a choking sensation, dizziness, and palpitation. There was no history of congestive failure.

Physical examination was negative except for moderate obesity, generalized arteriosclerosis, some increase in the anteroposterior diameter of the chest, occasional coarse crackles at the lung bases, and moderate cardiac enlargement. The blood pressure was 115/85.

Laboratory Studies.—The urine was negative, with a maximal specific gravity of 1.028. The erythrocyte count was 5,300,000, with a hemoglobin of 80 per cent. The leucocyte count was 9,100, with a normal smear and differential count. The fasting blood sugar was 99, nonprotein nitrogen 33, and cholesterol 297, mg. per cent. The stool was normal. The blood Hinton and Kahn reactions were negative. Electrocardiogram showed normal rhythm, rate 100, left axis deviation, P-R interval 0.20 second, notched, widened, and slurred QRS waves, prominent Q_2 and Q_3, and depressed S-T. Roentgenograms of the heart showed a transverse diameter of 17.3 cm.; the chest was 30.9 cm. in diameter; the left ventricle was prominent. The basal metabolic rate was –15 per cent.

CASE 2.—A 57-year-old housewife had a history of hypertension; this was discovered twenty years previously, when she sought medical advice because of headaches and dizziness. The past history also revealed gaseous distension for years, and nocturia for two years. Four years before the present study, she had an attack of severe, persistent, prostrating precordial pain, radiating to the back, left shoulder, and left hand, and requiring morphine. Another similar attack occurred a month later, this time with the development of dyspnea and râles in the chest, both of which were only transitory. A third severe attack, followed by transitory pericarditis and paroxysmal auricular fibrillation, occurred three years before the present study, and was followed by ten months of bed rest because of ten to twelve daily, mild attacks of pain in the precordium, neck, jaw, ear, left shoulder, and left arm. These decreased in frequency after that time to three to five a week, at which level they remained. A year before the present study, palpitation began to occur with the pain. Six months later an attack of fever, with cough and knifelike pleuritic pain, occurred, and left her with a slight cough. Two months before the present study, the fourth severe attack of precordial pain was noted. There was no history of congestive failure.

Physical examination was negative except for moderate cardiac enlargement, generalized arteriosclerosis, an apical systolic murmur, a few coarse crackling râles, and a snapping aortic second sound. The blood pressure was 160/90.

Laboratory Studies.—The urine showed a maximal specific gravity of 1.032. Mild glycosuria was present, but the urine was otherwise normal. The erythrocyte count was 5,400,000, with a hemoglobin of 80 per cent. The leucocyte count was 8,600, with a normal smear and differential count. The stool was normal. The blood nonprotein nitrogen was 19, and the fasting blood sugar ranged between 161 and 292, mg. per cent. The blood Kahn and Hinton reactions were negative. Electrocardiogram revealed normal rhythm, rate 85, left axis deviation, prominent Q_1, deep S_2, and flat T_1. Roentgenogram of the heart revealed a transverse diameter of 14.5 cm.; the chest was 24.2 cm. in diameter; the left ventricle was prominent. The basal metabolic rate was –3 per cent.

CASE 3.—A 57-year-old housewife had a family history of hypertension, a past history of nocturia for years, hypertension of seven years' known duration, and a cholecystectomy two years before the present study. Six years previously she first noted the onset of a squeezing precordial pain, associated with a choking sensation, and radiating into the left upper arm, which was brought on by exertion, excitement, or exposure to cold, and was relieved by rest and nitroglycerin. These attacks greatly curtailed her activity. Six months before this study she had a severe, prolonged attack, requiring morphine. Following this, the mild attacks became more frequent, extended over the entire chest, and radiated down both arms. There was no history of congestive failure.

Physical examination was negative except for generalized arteriosclerosis, slight cardiac enlargement, a basal systolic murmur, and a healed right upper quadrant scar. The blood pressure was 160/100.

Laboratory Studies.—The urine was negative, and showed a maximal specific gravity of 1.032. The erythrocyte count was 4,500,000, with a hemoglobin of 80 per cent. The leucocyte count was 9,000, with a normal smear and differential count. The stool was normal. The fasting blood sugar was 82, the nonprotein nitrogen 35, and the cholesterol 260, mg. per cent. The blood Hinton and Kahn reactions were negative. Electrocardiogram showed normal rhythm, rate 70, left axis deviation, depressed $S\text{-}T_{1, 2, 4}$, elevated $S\text{-}T_3$, inverted T_3, and inverted P_3. Roentgenogram of the heart revealed a transverse diameter of 13.8 cm.; the chest measured 27.8; the left ventricle was prominent and, on fluoroscopy, showed evidence of infarction; the aorta was somewhat calcified. The basal metabolic rate was –11 per cent.

CASE 4.—A 59-year-old tailor had had nocturia for several years. Five years before the present study, he first noted the appearance of a burning sensation above the left elbow, not associated with anything at all; this disappeared after six months. Six months later it recurred, this time associated with a similar pain in the left upper arm and a squeezing sensation in the chest and upper abdomen, all brought on by walking 100 yards. The pains were more frequent in winter, but averaged about ten a day through the year. Six months before the present study, the pain became more frequent and severe, so that dressing, eating, and moving about in bed brought it on; it was commonly associated with a feeling of shortness of breath when precipitated by more prolonged exertion. He used 2,200 nitroglycerin tablets during this six-month period. In addition, in the three and one-half years preceding the present study, he had noted pain in the calves, which was worse in winter, brought on by walking and relieved by standing still.

Physical examination was negative except for moderate obesity, arteriosclerosis, an increase in the anteroposterior diameter of the chest, slightly prolonged expiration, an apical systolic murmur, moderately cold and cyanotic feet, and poor arterial pulsations in the feet. The blood pressure was 150/100.

Laboratory Studies.—The urine was negative, and showed a maximal specific gravity of 1.030. The erythrocyte count was 4,850,000, with a hemoglobin of 75 per cent. The leucocyte count was 8,000 with a normal smear and differential count. The stool was normal. The fasting blood sugar was 93, and the nonprotein nitrogen was 34, mg. per cent. The blood Hinton and Kahn reactions were negative. Electrocardiogram revealed normal rhythm, rate 75, left axis deviation, depressed S-T_1, inverted T_1, and deep S_2. Roentgenogram of the heart showed a transverse diameter of 14.7 cm.; the chest measured 30.0 cm.; the left ventricle was prominent and the aorta tortuous. The basal metabolic rate was –4 per cent.

Case 5.—A 56-year-old housewife, whose father died of heart disease and one of whose sisters had hypertension, had a history of frequent sore throats in childhood, mastoidectomy at 20 years of age, hysterectomy at 44 years of age, intolerance of fatty foods for years, and pains in the large joints for eight years. Four years before the present study, she was troubled with nosebleeds and frontal headaches and was found to have hypertension. A short time later she began to experience a sense of painful pressure in the precordium, spreading to the left shoulder and arm, and occasionally to the scapula, precipitated by a walk of 250 to 300 yards, or by climbing up a flight of stairs. It was worse in cold weather, associated with a feeling of inability to catch her breath, lasting a few minutes, and followed after its disappearance by soreness over the precordium. Although her activities were considerably limited, she was able to do her housework. There was no history of congestive failure.

Physical examination was negative except for moderate obesity, arteriosclerosis, slight enlargement of the heart, and Heberden's nodes. The blood pressure was 150/90.

Laboratory Studies.—The urine showed a maximal specific gravity of 1.018; albumin and sugar were not detected, but occasional erythrocytes and leucocytes were noted in the sediment. The erythrocyte count was 4,750,000, with a hemoglobin of 80 per cent. The leucocyte count was 7,800, with a normal smear and differential count. The stool was normal. The fasting blood sugar was 125, the nonprotein nitrogen, 39, and the cholesterol 297, mg. per cent. The blood Hinton and Kahn reactions were negative. Electrocardiogram showed normal rhythm, rate 70, left axis deviation, deep S_2, and notched QRS_3. Roentgenogram of the heart showed a transverse diameter of 13.8 cm.; the chest measured 27.7 cm.; the left ventricle was prominent. Graham test showed poor filling of the gall bladder. The basal metabolic rate was –2 per cent.

Case 6.—A 56-year-old unemployed man, one of whose brothers had heart disease, had a history of gonorrhea forty years previously, and had been partly deaf for some years. Seven years before the present study, he suddenly experienced a tearing sensation to the left of the sternum. Since then a similar pain came on with exertion, excitement, or eating; later, it radiated to the left scapula and down the arm to the wrist, and was associated with a choking sensation. The frequency of his attacks required that he take 20 to 30 nitroglycerin tablets daily; he was bedridden

most of the time. The frequency of his attacks diminished two years before this study to about fifteen per day, requiring 100 nitroglycerin tablets weekly, and he was able to leave the house from time to time. He had occasional attacks of pain while at rest or asleep. One year before the study, a left-sided paravertebral alcohol injection from D_2 to D_5 was done; some of the thoracic manifestations of angina disappeared, but the number of attacks was not changed. After this procedure, he developed severe neuritis over the chest, and a few basal râles were noted. There was no history of congestive failure.

Physical examination was negative except for moderate obesity, generalized arteriosclerosis, an increase in the anteroposterior diameter of the chest, and a few basal râles. The blood pressure was 140/85.

Laboratory Studies.—The urine was negative, and showed a maximal specific gravity of 1.030. The erythrocyte count was 4,950,000, with a hemoglobin of 80 per cent. The leucocyte count was 8,100, with a normal smear and differential count. The stool was normal. The fasting blood sugar was 109, the nonprotein nitrogen, 32, and the cholesterol 328, mg. per cent. The blood Hinton test was negative and the Kahn test was doubtful. Electrocardiogram showed normal rhythm, rate 75, left axis deviation, deep S_2, and inverted, monophasic QRS_1. Roentgenogram of the heart showed a transverse diameter of 15.2 cm.; the chest measured 31.8 cm. The basal metabolic rate was –22 per cent.

TABLE I

CASE	CARDIAC OUTPUT (L./MIN.)	CARDIAC INDEX	ARTERIO-VENOUS O_2 DIFFERENCE (VOL. %)	CIRCULATION TIME (SEC.)	VENOUS PRESSURE (CM. H_2O)	VITAL CAPACITY (C.C.)	ARTERIAL PRESSURE (MM. HG)	CARDIAC ENLARGEMENT
1	3.3	1.9	5.85	22	3.5	2350	115/85	+
2	2.7	2.0	5.95	18	8.0	1600	160/90	+
3	3.7	2.1	5.00	18	6.0	1750	160/100	+
4	3.8	2.0	6.15	16	8.1	2800	150/100	0
5	3.8	2.2	5.80	13	9.1	--	150/90	+
6	3.5	1.8	5.60	20	3.8	2800	140/85	0
7	--	--	--	19	8.0	3600	140/95	0
8	--	--	--	17	4.2	2000	165/95	0
9	--	--	--	22	10.9	3750	110/70	+
10	--	--	--	17	9.7	3600	145/85	0
11	--	--	--	15	5.7	--	115/75	0
12	--	--	--	16	4.6	2200	180/110	0
13	--	--	--	19	3.4	2500	170/120	+
14	--	--	--	21	--	3300	140/80	0
15	--	--	--	17	8.4	2000	145/80	+
16	--	--	--	15	5.0	2650	130/80	0
17	--	--	--	13	3.2	--	120/70	0
18	--	--	--	14	5.0	3400	160/100	0
19	--	--	--	17	3.5	3500	190/100	+
20	--	--	--	16	--	2850	140/80	0
21	--	--	--	16	7.2	3850	180/90	0
22	--	--	--	21	3.4	4100	160/110	0

OBSERVATIONS

The cardiac index was within the normal range[5] of 2.2 ± 0.3 liters/minute/square meter of body surface in five of six instances; the apparently low value in Case 6 was associated with a basal metabolic rate

of –22 per cent. The arteriovenous oxygen difference was within normal limits in every case.

Values for circulation time were within the normal range of 12 to 19 seconds in all but five patients (Cases 1, 6, 9, 14, and 22). Three of these (Cases 1, 6, and 14) had basal metabolic rates at or below –15 per cent, and a fourth (Case 9) had polycythemia vera.

Normal values for venous pressure were found in all patients.

The arterial blood pressure was at or above 150/90 in about half the cases. In most instances the elevations in blood pressure were slight.

A decrease in vital capacity, usually slight, was found in all instances but one (Case 22).

DISCUSSION

In 1935, Starr and Gamble,[6] summarizing their studies with the ethyl iodide method, stated that the cardiac output was normal in patients with angina pectoris. Later, Bazett, et al.,[7] using a method based on pulse wave velocity, reported a normal cardiac output in one patient (Case 9 of their series) with uncomplicated angina pectoris. The results of the present study are in accord with these earlier observations: the volume and velocity of the circulation are normal. Somewhat slowed circulation times, associated with low metabolic rates, were found in three patients of the present study, including one whose cardiac index was also slightly decreased. Another patient with somewhat slowed velocity of blood flow had polycythemia vera. It is concluded that the slight slowing of blood flow seen in a few instances was due to metabolic or other noncardiac factors. Bernstein and Simkins[26] also observed that angina pectoris does not affect the circulation time. The low vital capacities of most of our patients are to be ascribed to age, obesity, and a short, stocky build, rather than to pulmonary congestion, for no signs or symptoms suggestive of the latter were detectable. The only common abnormality in cardiovascular dynamics was a slightly elevated arterial blood pressure in half of the patients; a similar incidence of hypertension has been reported by other authors.[8]

It is difficult to reconcile the observations on cardiac output and circulation time described in the past by other authors, as well as those reported here, with the recently published results of Starr and Wood.[9] These authors, using the ballistocardiograph to estimate cardiac output, found normal values in only five patients with angina pectoris, and low values in nineteen, including fifteen whose cardiac output was 30 to 60 per cent below normal. Four of the latter group developed congestive failure while under observation, but no such complicating factor was present in the others. Accordingly, other explanations must be invoked to explain the markedly subnormal cardiac output in these patients. One criticism of studies of the minute volume output of the heart by means of the ballistocardiograph is that they afford no information on the relation of the volume of the cardiac output to the metabolic require-

ments of the body. The utility of expressing cardiac output in terms of oxygen consumption was recognized by even the earliest authors.[10-12] Later workers have also emphasized the parallelism between metabolism and circulation, Grollman,[5] by relating the latter to surface area, and Starr, et al.,[13] by again pointing out its relation to oxygen consumption. It is clear, therefore, that the value of data on cardiac output is impaired by the absence of corresponding data on metabolism; this is especially true in patients with angina pectoris, since many of them have low metabolic rates.[8] The weight of the evidence appears to favor the conclusion that, except for arterial hypertension in many, the general circulation is normal in relation to metabolic requirements at rest and in the absence of anginal pain in patients with angina pectoris. It is apparent, therefore, that studies of this sort afford no explanation as to the mechanism of the occurrence of angina.

The anatomic cause of angina pectoris, namely, disease of the coronary arteries or their ostia, has been clearly defined.[14] In everyday life, attacks of angina pectoris commonly occur at times when the cardiac output is increased, i.e., during exertion or emotional upsets, or after heavy meals. Starr, Donal, and Collins[15] found that the cardiac output was increased in two patients during attacks of angina which were precipitated by emotion in one, and by the injection of epinephrine in the other. Both the former[16] and the latter[17-20] factors have been shown to increase cardiac output. It is not valid, however, to conclude that attacks of angina pectoris are in every instance associated with increased cardiac output. For instance, sympathomimetic amines, such as paredrine, which elevate blood pressure but do not increase cardiac output,[20] may cause anginal pain in patients with a history of angina pectoris.[21] It is clear from the formula of Evans and Matsuoka,[22] $W = OP + \frac{wV^{2*}}{2g}$, that an increase either in cardiac output or in blood pressure increases the work of the heart, and accordingly it may be concluded that the occurrence of angina pectoris is usually related to increased cardiac work. On the other hand, angina may occur when the work of the heart is not increased, i.e., during exposure to somewhat reduced atmospheric oxygen tensions,[23] or even when cardiac work is actually decreased, i.e., in cardiac arrhythmias with marked tachycardia.[24] The factor responsible for angina in these situations appears to be myocardial anoxia, consequent, in the one, to inadequate oxygenation of arterial blood, and in the other, to inadequate flow through the coronary tree which results from shortening of diastole. A valid generalization based on physiologic data is a reaffirmation of the clinical con-

*W — Work.
O — Output per minute.
P — Mean blood pressure.
w — Weight of blood.
V — Velocity of blood in aorta.
g — Gravitational constant.

cept that factors which increase cardiac work or decrease myocardial oxygenation lead to angina in patients with disease of the coronary arteries or their ostia, although reflex mechanisms are also of importance in many patients.[25]

SUMMARY AND CONCLUSIONS

1. Studies of the circulation were made on twenty-two patients with a history of angina pectoris, but with no signs or symptoms of congestive failure, cardiac arrhythmia, or valvular disease.

2. The cardiac output and circulation time were normal in relation to the metabolic requirements. When slowing of the circulation occurred, it was because of noncardiac factors.

3. The venous pressure was normal in all instances.

4. The only common abnormality of cardiovascular dynamics was arterial hypertension.

5. The relation of available physiologic studies of the circulation to the occurrence of attacks of angina is discussed; it is concluded that a valid generalization based on physiologic data is a reaffirmation of the clinical concept that factors which increase cardiac work or decrease myocardial oxygenation lead to angina in patients with disease of the coronary arteries or their ostia, although reflex mechanisms are also of importance in many patients.

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CRITICAL EVALUATION OF CARDIAC MENSURATION IN THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE

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THE reciprocal activity of sodium and desoxycorticosterone acetate in maintaining the patient with Addison's disease has been previously demonstrated, according to the equation $Na \times D = k$, where Na represents the daily ingestion of sodium in grams, D, the daily requirement of desoxycorticosterone acetate in milligrams, and k, a constant for which, in eight patients, values between 30 and 45 have proved satisfactory.[1-4] In all of these studies, cardiac mensuration has been used as an index of the degree of sufficiency of the treatment, and it has been found that, within limits, the size of certain cardiac measurements, notably the cardiothoracic ratio, frontal cardiac area, and total cardiac volume, vary directly with the condition of the patient. In other words, as the patient improves, a concomitant increase occurs in the proportions of the abnormally small heart associated with untreated Addison's disease. This point is well illustrated in Fig. 1, in which it is shown that the cardiac measurements varied directly as the product of the amount of sodium and desoxycorticosterone acetate ingested, and the degree to which this particular patient was symptomatically controlled. Such significant observations have been duplicated to a greater or lesser degree in all of our cases.

It is our present purpose to emphasize the limitations of cardiac mensuration as a guide to the amount of desoxycorticosterone acetate and sodium which should be administered to any patient with Addison's disease at a given time.

Some 200 observations of cardiac size in thirteen patients with Addison's disease served as a basis for the study. Eight of these patients have been seen in crisis, and followed under treatment with desoxycorticosterone acetate and measured amounts of sodium for periods varying from twenty weeks to four years.

As in previous work, the cardiothoracic ratio, the frontal cardiac area (sq. cm.), and the heart volume (c.c./M^2 body surface) have been taken as indices, and averaged values have been obtained for the thirteen patients as follows: in crisis, 0.35, 84, and 314, respectively; in

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states of insufficiency, 0.39, 96, and 390, respectively; and in the adequately treated patient, 0.46, 122, and 480, respectively.

The cardiothoracic ratio, the frontal cardiac area, the cardiac volume, and the body surface area have been estimated by methods previously described.[1]

Criteria for the recognition of states of crisis, insufficiency, stabilization, and overtreatment have been fully given elsewhere.[1, 4, 5]

The ability of desoxycorticosterone acetate and sodium to alter cardiac size in a quantitative manner has definite limitations in actual practice:

1. There are faults inherent in the methods of mensuration necessarily employed in vivo. The technique of taking roentgenograms must be as nearly uniform as possible. In the present series of cases we have discarded more than seventy films as being unfit for comparison for this reason alone. Moreover, difficulty is encountered in actively delineating the frontal cardiac area, in ascertaining the actual geometric configuration of the heart, and so forth. These problems have already been discussed in greater detail.[1, 4]

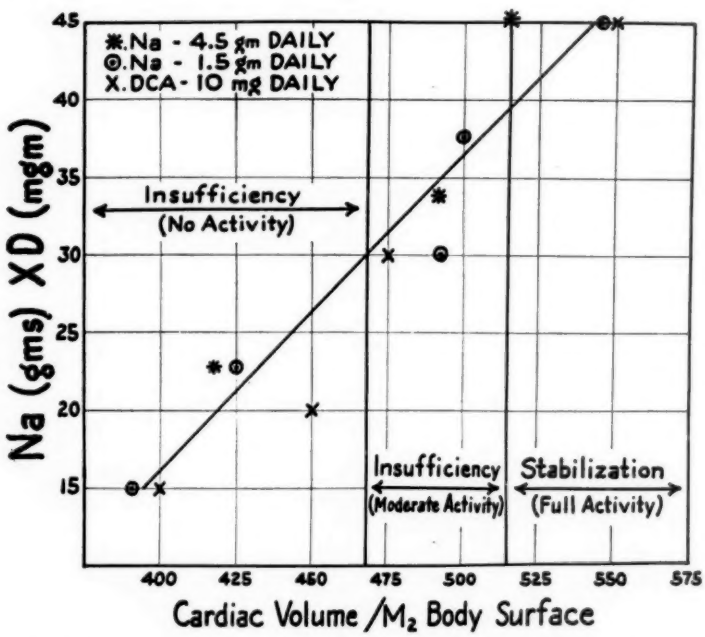

Fig. 1.—Effect of varied products of Na X D on heart size in relation to control of Addison's disease.

2. Measurements of the heart vary widely from person to person, so that no yardstick covering all cases can be made. For example, composite measurements of two patients are contrasted in Table I.

It appears inevitable that each patient must serve as his own control. If such a plan is followed, the percentual changes upward or downward in subsequent measurements have been found to correspond

TABLE I

PATIENT	C. T. R.	F. C. A.	HEART VOL./M² BODY SURFACE
	Crisis or Impending Crisis		
K. K.	0.26	66	236
M. C.	0.31	79	282
	Insufficiency		
K. K.	0.35	85	299
M. C.	0.39	96	367
	Stabilization		
K. K.	0.42	119	426
M. C.	0.47	125	461

roughly with the clinical condition of the patient and the degree to which the disease is controlled by sodium and desoxycorticosterone acetate.

3. When crisis is adequately treated with salt or with salt and desoxycorticosterone acetate, the size of the heart will increase rapidly until blood volume is restored. This may be accomplished entirely by the use of salt, provided a sufficient amount and concentration are given. Apparently the reduced blood volume is partly responsible for the small heart of Addison's disease, as demonstrated earlier.[1, 4]

4. Immediately after crisis has been controlled, products of sodium and desoxycorticosterone acetate much beyond 45 may be, and have been, used for considerable periods of time without producing an enlargement of the heart to critical proportions. The data in Table II are illustrative.

TABLE II

VARIATIONS IN RESPONSE TO HORMONE IN, AND IMMEDIATELY FOLLOWING, CRISIS, AS RELATED TO CARDIOTHORACIC RATIO

PATIENT	DAILY INTAKE OF		PRODUCT	NUMBER OF DAYS USED	C.T.R.	
	NA (GM.)	DCA. (MG.)			BEFORE	AFTER
E. M.	11.0	10	110	14	0.33	0.45
J. F.	3.0	15	45	21	0.38	0.39
	3.0	20	60	7	0.39	0.45
	3.0	25	75	17	0.45	0.51
H. L.	10.7	10	107	9	0.46	0.58
H. L.	2.5	25	63	19	0.40	0.52
K. G.	3.0	15	45	14	0.34	0.35
	3.0	20	60	7	0.35	0.37
	3.0	25	75	7	0.37	0.40
M. C.	4.5	15	68	12	0.31	0.36
	4.5	15	68	7	0.36	0.36
	3.1	25	75	4	0.36	0.40

It will be noted that products of Na and D varying from 60 to 110 have been used for intervals of four to twenty-one days without causing cardiac failure. The exception to this statement is Patient H. L., who received 10.7 Gm. of sodium and 10 mg. of desoxycorticosterone acetate daily for nine days, at the end of which time she developed

widespread peripheral edema and congestive cardiac failure with pulmonary edema. The great variation in response of the individual patient is still further reflected in the cardiothoracic ratios, which, in one instance (M. C.), remained stationary over a seven-day period on a sodium-desoxycorticosterone acetate product of 68. These differences in reaction cannot be attributed entirely to variations in the clinical condition of the patients, at least in so far as we are able to measure it. For the present, it seems to be important to emphasize the variation and to utilize increasing heart size in the individual case as an end point in ascertaining when and to what extent the dosage of drug and the allowance of sodium shall be changed.

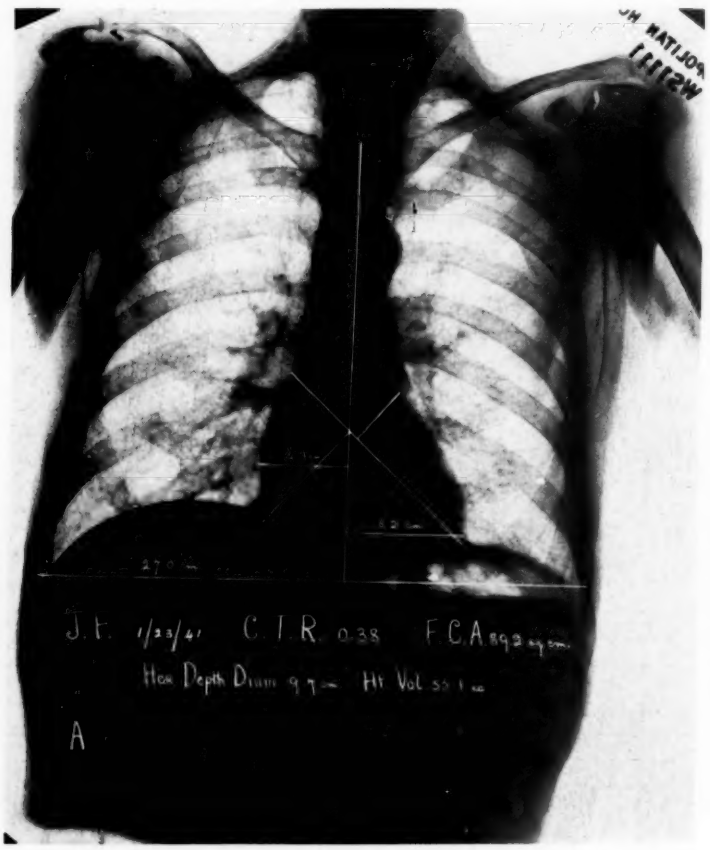

Fig. 2A.—J. F. Patient in crisis. Note the relatively large cardiac measurements as compared with Fig. 2B.

5. In two patients (J. F. and E. M.), the cardiac measurements have remained well within the normal range of values despite the onset of toxic symptoms, notably hypertension. In one of these two, very slight, transient, pretibial edema also occurred. In both instances the patients had been controlled and maintained at a sodium-desoxycor-

TABLE III

HYPERTENSION OCCURRING WITHOUT HEART FAILURE OR INCREASE IN CARDIAC SIZE

PATIENT	STABILIZED WEEKS	DAILY INTAKE OF		PRODUCT	C.T.R.*	B.P.
		NA (GM.)	DCA. (MG.)			
J. F.	18	3	15.0 S†	45	0.48	116/72
	38	5-7	4.8 P‡	75-105	0.49	210/110
E. M.	36	6	2.5 P‡	45	0.42	120/74
	90	1.5	30.0 S†	45	0.42	170/120

*C.T.R. = Cardiothoracic ratio.
†S = Oily suspension for intramuscular injection.
‡P = Pellet of crystalline material for subcutaneous implantation.

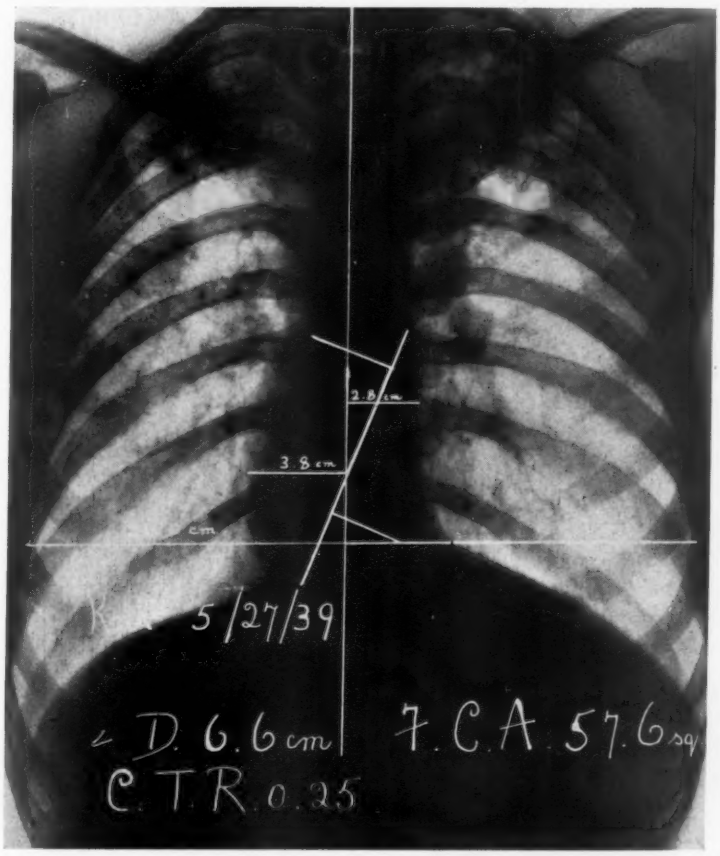

Fig. 2*B*.—K. K. Patient in crisis. Heart volume/M², body surface 236 c.c. Note contrast in the size of the hearts of the two patients illustrated, despite the same state of adrenal insufficiency.

ticosterone acetate level of 45 for relatively long periods of time: E. M. for 80 weeks and J. F. for 18 weeks (see Table III). In the eightieth week of treatment, E. M. was found to have changed his dietary slightly; he was ingesting approximately 3.75 Gm. of sodium instead of the prescribed 3 Gm. At the same time, he was receiving by absorption from implanted pellets of desoxycorticosterone acetate

the equivalent of 15 mg. daily of the drug by injection in sesame oil.* Inasmuch as he felt well and his cardiothoracic ratio had been long stabilized at approximately 0.42, he was allowed to continue this regime. Ten weeks later the blood pressure had risen to hypertensive levels, as noted in Table III, but the heart failed to show any evidence of further enlargement at this time. In the case of J. F., language difficulties were apparently responsible for his adding large quantities of salt to his food and not using the diet prescribed. He was not seen between the eighteenth and thirty-eighth weeks, during which time he dieted as he pleased and received, by absorption from implanted pellets, the equivalent of 15 mg. of desoxycorticosterone acetate daily by injection. From calculation of a week's menus and the rough estimation of salt intake, it is believed that he consumed between 5 and 7 Gm. of sodium daily, at least for the latter part of this period. The hypertension (210/110) was not reflected in any appreciable increase in the cardiac measurements over the period of time during which it existed. Four days after the sodium intake was regulated by using the previously prescribed 3 Gm. daily, the blood pressure fell to 120/82.

It is of special interest to note that this high product of sodium and desoxycorticosterone acetate (about 85) for a considerable period of time did not cause cardiac failure, whereas, in the earlier treatment of this patient, immediately after the relief of crisis, a ratio of 75 (3 Gm. of sodium and 25 mg. of desoxycorticosterone acetate) caused acute pulmonary edema and dilatation of the heart after daily use for two and a half weeks.

These observations lead us to the conclusion that overdosage in the well-controlled patient will not be detected early by increasing heart size, but is more likely to produce the syndrome of hypertension, with or without other concomitant phenomena, such as peripheral edema, weakness, or altered kidney function.

SUMMARY AND CONCLUSIONS

1. The changing size of the heart can be used within definite limits as an index of the respective amounts of sodium and desoxycorticosterone acetate that can be employed safely in the treatment of Addison's disease.

2. In general, cardiac measurements can be maintained within normal limits by a product of sodium in grams and desoxycorticosterone acetate in milligrams of 30 to 45; the actual figure is very constant for any individual patient.

3. In utilizing this rule, individual variations in cardiac size and errors inherent in the technical procedures for carrying out cardiac mensuration must be considered.

*For this and all the other patients, desoxycorticosterone acetate in sesame oil for injection and as sterile compressed tablets for implantation was furnished by Dr. Max Gilbert, of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.

4. This rule is not applicable to (a) patients in crisis and for short periods after the control of crisis; at such times, larger products of sodium and desoxycorticosterone may be used with relatively small upward alterations in the cardiac silhouette; (b) patients under control for long periods of time who inadvertently or purposely utilize more than the prescribed amount of either sodium or desoxycorticosterone acetate, or both, despite which the cardiac measurements may remain well within normal limits, while hypertension or other toxic symptoms appear.

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PRODUCTION OF NEPHROSCLEROSIS AND CARDIAC HYPERTROPHY IN THE RAT BY DESOXYCORTICOSTERONE ACETATE OVERDOSAGE

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SOME time ago it was found[1] that testosterone and other testoid compounds increase the size of the renal tubules and induce hypertrophy of the cells lining the parietal lamina of Bowman's capsule. Kidneys thus stimulated by testosterone are not only morphologically, but even functionally, above normal, inasmuch as they exhibit an increased resistance against the damaging effect of sublimate[2, 3] or ureteral obstruction.[4] The literature concerning this so-called "renotropic" action of the steroids has recently been reviewed,[5, 6] and hence will not be considered here in detail. Suffice it to say that, although there is no complete interdependence between the renotropic and the testoid action of steroids, generally speaking, the two tend to run parallel.

A short time ago it was found that desoxycorticosterone acetate (DCA.) causes typical nephrosclerosis, accompanied by cardiac hypertrophy and other signs of hypertension, in young chicks.[7] This nephrosclerosis is especially readily obtained in chicks which receive comparatively high doses of sodium chloride in their drinking water.[8] Mammals, on the other hand, proved particularly resistant to this effect. Moderate degrees of nephrosclerosis were produced in one experimental series in the dog, monkey, and rat, and here again sodium chloride appears to have played some part in the production of the condition, for the animals received varying amounts of sodium chloride during certain periods of the desoxycorticosterone acetate treatment.[9] This nephroselerotic effect has not as yet been obtained with testosterone or any other testoid compound. It appears to depend upon the corticoid action of steroids, and, up to the present, has been detected only in desoxycorticosterone acetate, progesterone, and acetoxypregnenolone, whose nephrosclerosis-producing effect, as well as their corticoid potency, decreases in the order in which they are here mentioned. In view of the great clinical importance of nephrosclerosis and hypertensive heart disease, it appeared worth while to develop an experimental technique which would reliably produce such changes in mammals by overdosing them with adrenal cortical compounds. The object of the present communication is to report on such additional experiments,

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which revealed that marked cardiac hypertrophy and nephrosclerosis are readily produced in the rat by a suitable combination of desoxycorticosterone acetate and sodium chloride overdosage.

EXPERIMENTAL

Twenty male albino rats, weighing 76 to 105 grams (average 92 grams) at the onset of the experiment, were divided into two groups of ten each. The animals of the first group received 10 mg. of desoxycorticosterone acetate per day in two subcutaneous injections; the compound was administered in the form of a fine aqueous crystal suspension containing 50 mg. per cubic centimeter. This treatment was continued throughout the experiment, but, after ten days of desoxycorticosterone acetate administration, the drinking water of both groups was substituted by a 1 per cent sodium chloride solution. Thus, the administration of salt was identical in the experimental and control groups, but only the former received desoxycorticosterone acetate. Treatment with this steroid was continued for a period of two months, during which time seven of the injected animals succumbed with signs of marked nervous disturbances. Most of them showed varying degrees of tremor and hyperirritability, and, in some of them, certain muscle groups became paralyzed. This was particularly obvious in one rat, which became quite unable to move the extensor muscles of one forepaw. Similar nervous disturbances in animals receiving desoxycorticosterone acetate in combination with sodium chloride have been described previously,[9] but since they are not very relevant to the problem under discussion, we do not propose to discuss them here in more detail. It is noteworthy, however, that all the animals which succumbed during the experimental period showed varying degrees of nephrosclerosis and cardiac hypertrophy. These lesions were even more pronounced in the three surviving animals, which were autopsied at the end of the two-month treatment period.

The most striking change observed in the desoxycorticosterone acetate group was an enormous enlargement of the kidneys, the surface of which was mottled and rather irregular (Fig. 1). A cross section through the kidneys, viewed at low magnification (Figs. 2 and 3), revealed that the renal papilla remained normal in size and the medulla showed only slight structural abnormalities, whereas the cortex was approximately twice as wide as that of the control animals, and exhibited great irregularities due to patches of sclerosis, obstruction of tubules by casts, etc. Under higher magnification, in many instances, wedge-shaped areas of dense sclerosis were noticeable (Fig. 4). Throughout the kidney, most of the glomeruli were sclerosed. The tuft capillaries exhibited marked hyalinization, and masses of proliferating epithelioid cells surrounded the glomeruli. The stroma was infiltrated by small round cells, or consisted of thick bands of dense connective tissue. The frequently dilated tubules contained many hyaline casts

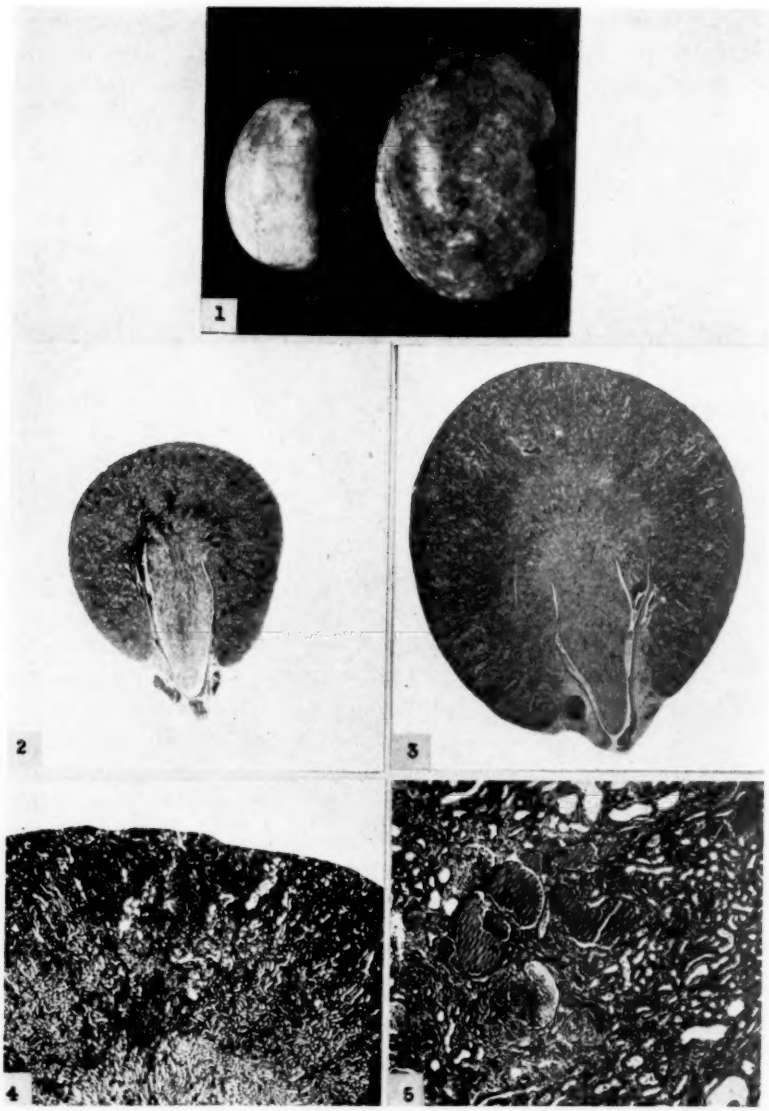

Fig. 1.—Macroscopic view of normal kidney of animal which received sodium chloride only (left), and greatly enlarged, mottled kidney of animal which received sodium chloride plus desoxycorticosterone acetate (right).

Fig. 2.—Low magnification view of cross section through kidney of normal rat which received sodium chloride only.

Fig. 3.—Low magnification view of cross section through kidney of animal which received sodium chloride plus desoxycorticosterone. Note that the renal papilla is approximately normal in appearance, whereas the cortex is greatly enlarged and exhibits an irregular pattern due to dilatation of cast-filled tubules and patches of sclerosis.

Fig. 4.—A V-shaped sclerotic area in the renal cortex of a desoxycorticosterone acetate treated rat.

Fig. 5.—Several dilated renal tubules containing hyaline casts and one sclerotic glomerulus surrounded by epithelioid cell proliferations. Same animal as that shown in Fig. 4.

(Fig. 5). Frozen sections stained with sudan III revealed lipid depositions in the proximal convoluted tubules and in many of the sclerotic glomeruli, as well as in a few of the casts. Some of the medium-sized arterioles were likewise rich in lipid granules and showed marked proliferation of the fibromuscular elements of their walls. In general, the appearance was that of the "large white kidney" in the process of being transformed into the nephrosclerotic kidney, although the secondary contraction of the organ had not progressed far enough to compensate for the initial enlargement.

The heart was likewise greatly enlarged in all the desoxycorticosterone acetate treated animals, and, on cross section under low

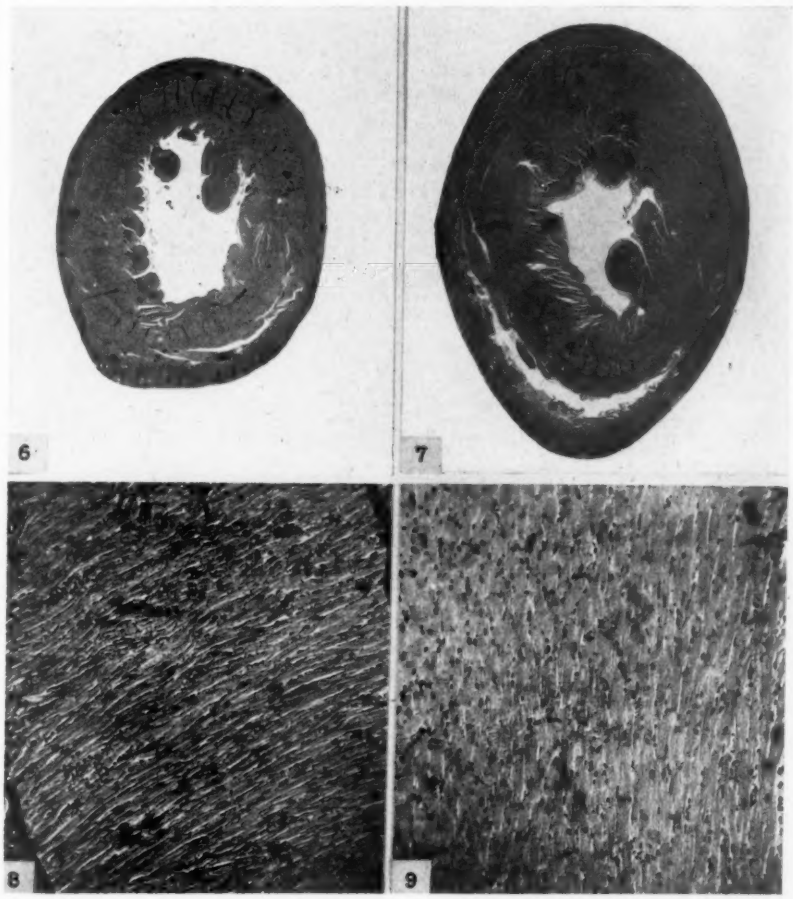

Fig. 6.—Cross section through the ventricles of the heart of normal control rat which received sodium chloride alone.

Fig. 7.—Cross section through the ventricles of the heart of a rat which received sodium chloride plus desoxycorticosterone acetate. Same magnification as Fig. 6. Note the great increase in the thickness, especially of the left ventricle.

Fig. 8.—High magnification of a section through the left ventricle of the heart shown in Fig. 6.

Fig. 9.—Section through the left ventricle of the heart shown in Fig. 7. Same magnification as Fig. 8. Note the great increase in the width of the muscle fibers.

magnification, it appeared that both the right and the left ventricles partook in this hypertrophy, although the change was much more obvious in the latter (Figs. 6 and 7). Under high magnification (Figs. 8 and 9), it became evident that the enlargement of the heart was not due merely to edema, but was caused by actual increase in the width of the individual fibers. The enlargement of the heart and kidneys is even more striking if we consider that the body weight of the desoxycorticosterone acetate treated animals was far below normal because treatment interfered with their normal growth. Table I gives the average body and organ weights (with the range in brackets) of the desoxycorticosterone acetate treated and control animals at the end of the experiment, that is to say, after two months of treatment. It will be noted that, since seven of the desoxycorticosterone acetate treated animals died earlier during the experimental period, the weights of these had to be eliminated from the averages because they were not comparable to the remaining treated and the control rats, all of which were killed on the same day.

TABLE I

EFFECT OF DESOXYCORTICOSTERONE ACETATE ON ORGAN AND BODY WEIGHTS OF RATS SENSITIZED BY SODIUM CHLORIDE ADMINISTRATION*

	CONTROLS	DCA. TREATED
Body weight	226 (185-265)	176 (145-180)
Kidneys	1.75 (1.3-2.0)	3.41 (2.9-4.4)
Heart	0.89 (0.82-1.0)	1.36 (1.34-1.37)
Spleen	1.1 (0.6-1.6)	2.49 (1.82-2.96)

*All weights are expressed in grams.

It should be emphasized that the changes which occurred in these rats could not have been due to the desoxycorticosterone acetate itself, for they were never observed in the numerous experiments performed in this laboratory with desoxycorticosterone acetate on rats which were receiving a normal sodium chloride intake. This does not mean that the steroid cannot cause any cardiorenal lesions on a normal salt intake, but merely that its effect on the above organs is greatly augmented by sodium chloride. It will be recalled in this connection that Darrow and Miller[10] noted necrosis of myocardial fibers in rats which were overdosed with desoxycorticosterone acetate and on a normal diet. Such lesions were not observed in our series. It should be emphasized also that, in the present experiments, the cardiorenal effects were not due to the sodium chloride per se, for the controls and the experimental animals received the same salt solution.

From the above experiments it appears that chronic treatment with desoxycorticosterone acetate in combination with a high sodium chlo-

ride intake causes marked renal changes and, probably as a result of the former, pronounced cardiac hypertrophy. It is suggestive to assume, therefore, that the rise in blood pressure which is known to follow desoxycorticosterone acetate overdosage in man, as well as in animals, may be secondary to the renal changes caused by this hormone. It is well to keep in mind, furthermore, that the increase in heart volume which often follows desoxycorticosterone acetate and sodium chloride treatment of patients with Addison's disease[11, 12] may be due partly, at least in chronically treated patients, to actual muscular hypertrophy and not merely to dilatation.

Our observations also indicate that adrenal cortical hyperactivity should be considered as a possible etiologic factor in the production of the so-called "renal hypertension" in man.

In the introductory section of this paper we mentioned the fact that, at least in the chick, nephrosclerosis and cardiac hypertrophy have also been produced with progesterone. Hence, it is tempting to assume that the hypertension which often develops in women during gestation may be related to the increased production of progesterone and similar steroids which is known to occur during this period. In any case, our observations give experimental support to the view that a derangement in the production or metabolism of steroids may play an important role in the pathogenesis of renal lesions that are conducive to hypertensive heart disease.

SUMMARY

Experiments on albino rats indicate that, if the sodium chloride intake is kept high, desoxycorticosterone acetate regularly produces nephrosclerosis, cast formation in the renal tubules, and hypertrophy of the renal arterioles, as well as marked cardiac hypertrophy. The significance of these observations is discussed in connection with their possible bearing on the cause of nephrosclerosis and hypertensive heart disease in man.

The expenses of this investigation were defrayed through a grant received from the DesBergers-Bismol Laboratories. The authors are also indebted to Dr. Erwin Schwenk of the Schering Corporation, of Bloomfield, N. J., who supplied the desoxycorticosterone acetate for these experiments.

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INTRAVENTRICULAR BLOCK WITH ECTOPIC BEATS APPROACHING NORMAL QRS DURATION

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THE occurrence in cases of intraventricular block of ectopic beats with ventricular complexes of normal duration or of a duration shorter than that of the sinus beat is rare. One such case was reported by Wilson and Herrmann,[1] who explained the phenomenon as follows: "The ventricular extrasystole (cycle A_2, Fig. 19) was of septal origin and reached both ventricles at about the same time, but it reached the right ventricle below the blocked area, and the form of the resulting ventricular complex is more nearly normal than that of the sequential ventricular complexes." It has been shown experimentally[2] that, in the dog's heart without intraventricular block, stimulation of the ventricular surface at the longitudinal sulcus produces complexes with normal QRS duration, whereas stimulation on either side of this region produces complexes with prolonged QRS duration.

A second case of bundle branch block with premature systoles of relatively normal form was reported by Hewlett,[3] who could offer no explanation for it other than that given by Wilson and Herrmann. In view of their frequent occurrence, Hewlett discards the idea that two stimuli arising simultaneously, one in each ventricle, could result in these premature complexes.

Because of the rarity of this phenomenon we are presenting three more such cases.

Case 1.—Five tracings were taken on this patient over a four-year period. Sinus rhythm was present in all of them. In the second, third, and fifth records (Figs. 1, *B*, 2, *A*, and 2, *B*), alternation of the P-P interval was present without changes in P-wave contour or P-R interval. In the first and fifth records (Figs. 1, *A* and 2, *B*), QRS was of normal duration (0.09 second) and of similar contour in corresponding leads. The third (Fig. 2, *A*) and fourth (not shown) records revealed intraventricular block of the common type, with a QRS duration of 0.16 second. The second record (Fig. 1, *B*) showed sinus rhythm with intraventricular block of the same type as in the third and fourth records, and, in addition, showed beats with a normal QRS duration which resembled those in the first and fifth (Figs. 1, *A* and 2, *B*) records. These apparently normal beats were seen in Leads II and CF_2, although in the latter only one such beat was present. In Lead II the first normal QRS was a premature systole, and the second followed at an R-R in-

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terval which was longer than that of the regular sinus rhythm. The second normal QRS was preceded by a P wave with a P-R interval of 0.16 second, which was 0.01 second shorter than that of the regular sinus beat. After a normal sinus beat, the sequence was repeated. The duration of QRS in these beats was 0.10 and 0.08 second, as opposed to 0.16 second for the QRS duration of the sinus beat with intraventricular block.

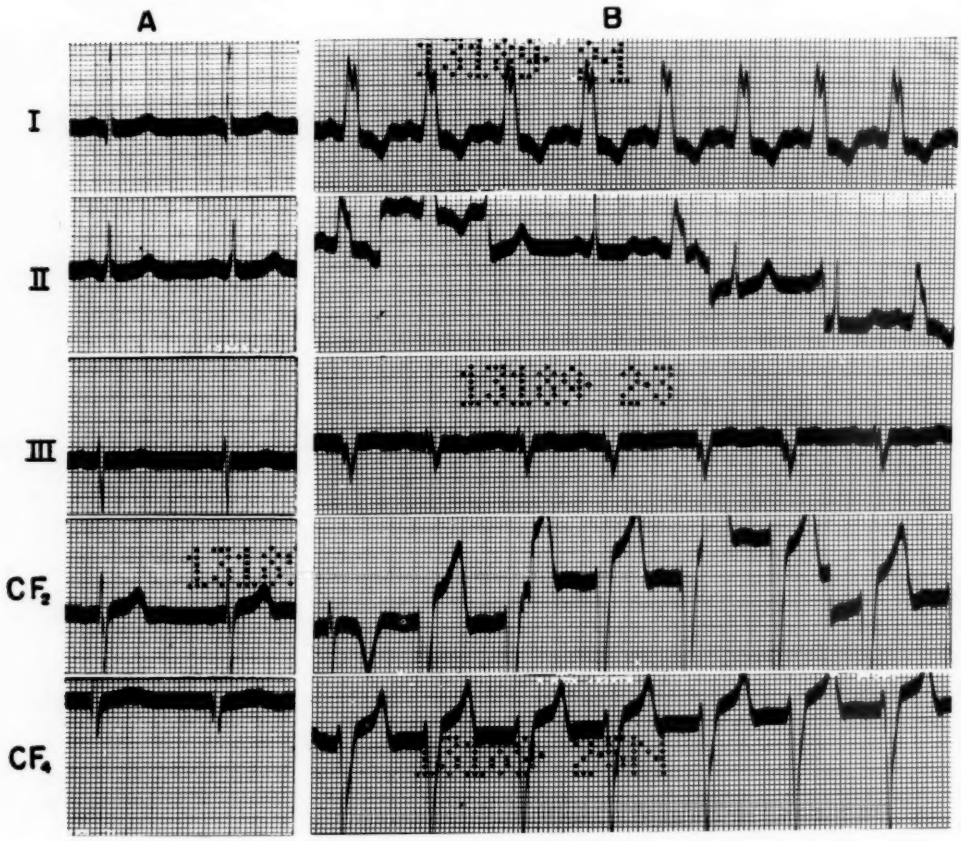

Fig. 1.—Case 1. Described and discussed in text.

The normal QRS duration of the premature beats in these records in the presence of intraventricular block can be explained in two ways: (1) by a certain localization of the site of ectopic impulse formation in relation to the region of bundle branch block,[1, 3] or (2) by a supernormal phase of recovery within the injured tissue, i.e., the region of intraventricular block. If the impulse arises within the septum at a point approximately equidistant from the two bundle branches, and enters the two bundle branch systems below the region of block, reaching both the right and left ventricles at the same time, the resulting QRS would appear normal in contour and duration. That this may have happened here is plausible because the QRS of the premature beat and the one following resemble in contour the beats of supraventricular origin in the control records (Figs. 1, *A* and 2, *B*). If, on the other hand, the

impulse arose above, instead of below, the region of block, presumably in the A-V node, and reached the region of block in the bundle branch system in the supernormal phase of recovery, so that it was conducted without delay, then a QRS of normal contour and duration would result.

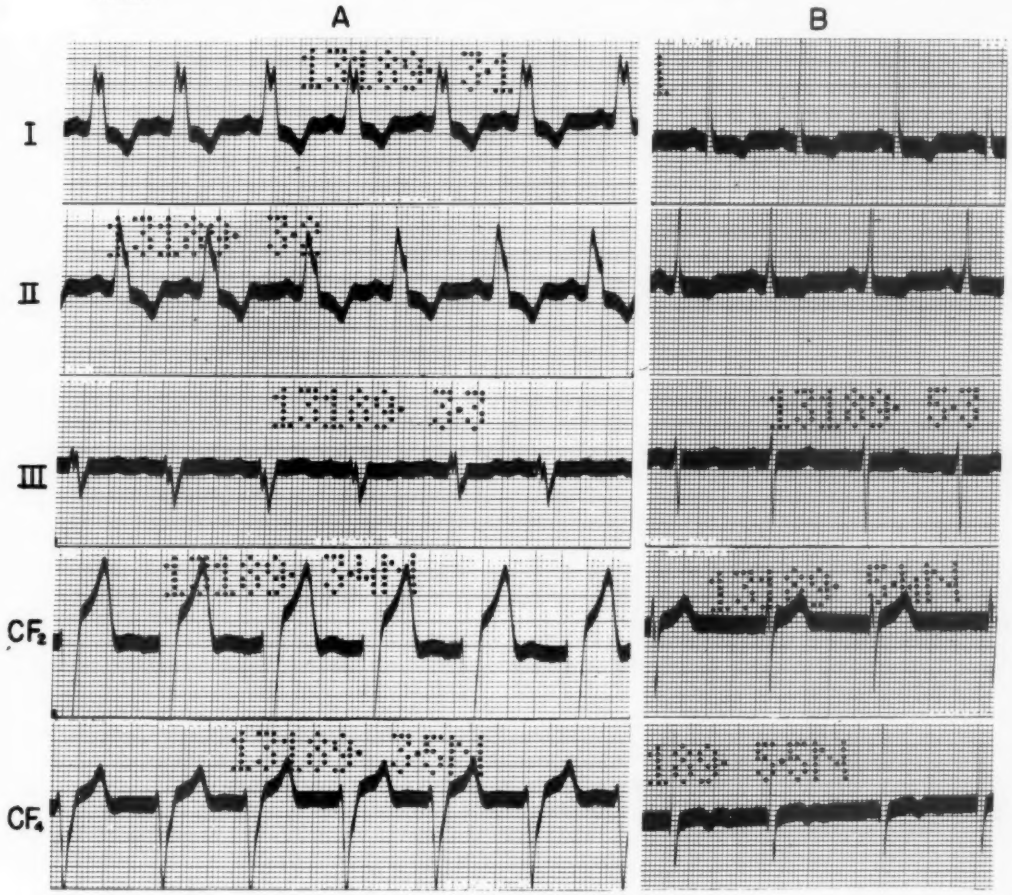

Fig. 2.—Case 1. Described and discussed in text.

The explanation of the second normal QRS invokes further mechanisms which were not considered in the explanation of the premature beat. It might, of course, be a second discharge from the same ectopic focus which gave rise to the premature beat. However, because the P-R of this second normal QRS is almost that of the normal sinus beat with intraventricular block, it is possible that this is a normally conducted sinus beat which arrived enough later in the injured tissues after the preceding impulse to permit their complete recovery and hence allow normal conduction. This presupposes that the block is reversible. Alternatively, the second beat with normal QRS duration may actually be a fusion beat. If this is the case, the impulse from the ectopic pacemaker must reach one bundle branch at the same time as the sinus impulse, and the other bundle branch before the sinus impulse reaches

or traverses the area of block. The S-T-T after the second QRS of normal duration was intermediate in contour between the S-T-T associated with the QRS of intraventricular block and that of the first QRS of normal duration; this lends credence to the idea of a fusion beat. However, the change in S-T-T configuration may be of no moment, because it is known that S-T-T changes occur after premature systoles.

Because the configuration of the QRS-T of the premature and following beats resembled that of the QRS-T at the time of undisturbed sinus rhythm without intraventricular block, the spread of the impulse through the ventricles under both circumstances was similar. This is in agreement with our assumption that the location of the ectopic impulse is such that it reaches both bundle branches at the same time, and below the level of the region of block.

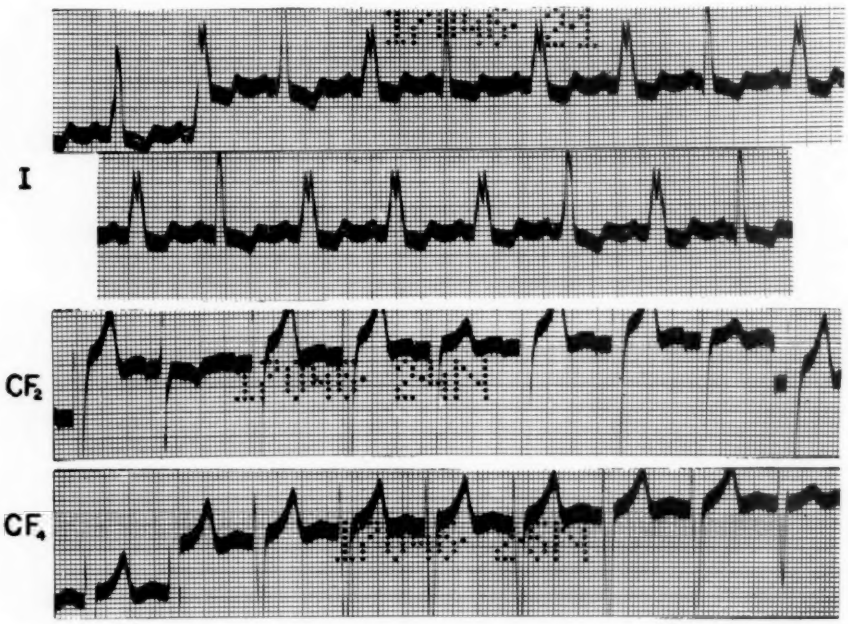

Fig. 3.—Case 2. Described and discussed in text. The first two segments are a continuous strip of Lead I.

The bigeminal rhythm which occurred in Figs. 1, *A*, 2, *A*, and 2, *B* was interpreted as due to (1) auricular premature systoles arising close to the S-A node, (2) premature systoles arising within the S-A node, or (3) alternation in S-A conduction time. The first possibility is not regarded as likely because of the identity of the P waves and P-R intervals in all beats. An exact differential diagnosis between the two remaining possibilities cannot be made; therefore, unless one wishes to assume alternation in S-A conduction, this would be an example of premature systoles arising within the sinus node. Ordinarily, the diagnosis of premature systoles of sinus origin is difficult to make, but in this instance the regular recurrence of the premature beats makes their recognition more definite.[4]

Case 2.—Five tracings were taken on this patient during an eight-month period. All five records showed sinus rhythm with intraven-

tricular block of the common type and a QRS duration of 0.16 second. The first three records showed premature systoles, not preceded by premature P waves, with a QRS duration shorter than that of the sinus beat. In the first (not shown) and third (Fig. 4) records the premature beats occurred just before, during, or after the sinus P wave, and there was a variation of as much as 0.14 second in the R-R interval of the premature beat and the preceding beat.

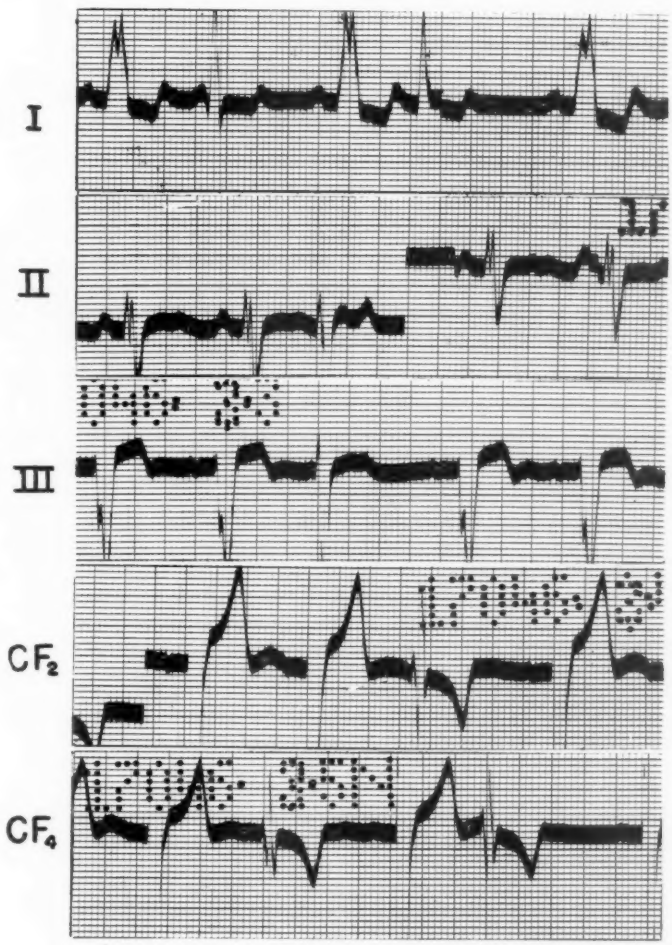

Fig. 4.—Case 2. Described and discussed in text.

In the second record (Fig. 3), of which only Lead I, CF_2, and CF_4 are available, the premature systoles occurred late in diastole and were preceded by the normal sinus P wave at a P to QRS distance which varied from 0.12 to 0.18 second. The P-R of the normal sinus beats measured 0.18, and the QRS duration, 0.16 second. The QRS duration of the premature beats varied from 0.09 to 0.13 second. The later in diastole the premature beat occurred, the longer its QRS became. This suggests that two pacemakers were controlling the heart during the time

of the premature beat. When the premature beat occurred early, the interference between the two took place above the bifurcation of the common bundle, so that the auricles were controlled by the sinus, and the ventricles by the ectopic, pacemaker; when the ectopic pacemaker discharged relatively later, the interference was below the bifurcation of the common bundle, so that the ventricles were stimulated by both pacemakers and a fusion beat resulted.

The interpretation of the records in Case 2 is similar in many respects to that of the records in Case 1. The premature beats probably arose from a focus within the interventricular septum, and spread equally to both bundle branch systems below the region of block. The possibility that an ectopic focus was situated above the region of block and gave rise to impulses which passed through the injured tissues (the region of block) during the supernormal phase cannot be entertained in interpreting this series of records because the beats with normal QRS duration occurred over a variable period in the cycle, from very early to just before the expected occurrence of the sinus beat. The presence of fusion beats when the R-R of the premature beat approached that of the sinus beat, while the sinus rhythm remained regular, is further evidence that a sinus pacemaker, plus an active ectopic pacemaker, was responsible for the variations in the electrocardiogram.

It is important to emphasize that, in sinus rhythm *without* intraventricular block, the same type of septal ectopic pacemaker may be operating, giving rise to premature beats which are indistinguishable from nodal premature beats. In the presence of block in the bundle branch system it is possible, as these two cases show, to have an ectopic pacemaker so located in the ventricle that it gives rise to ventricular complexes with normal QRS duration.

CASE 3.—Two records were taken, three months apart. The first record* (Fig. 5, *A*) shows sinus rhythm with intraventricular block of the common type. The duration of QRS is 0.16 second. Premature systoles from one focus, with a QRS duration of 0.14 second, which is less than that of the sinus beat, occur throughout the tracing. Depending upon the time of the arrival of these beats in the cardiac cycle, they are either interpolated or followed by a compensatory pause. In the second record (Fig. 5, *B*), auricular fibrillation is present. Most of the ventricular complexes correspond in contour and duration to the sinus beats in Fig. 5, *A*. In addition, there are beats of shorter QRS duration. These occur at both short and long intervals after a QRS which corresponds in contour and duration to the supraventricular beat in Fig. 5, *A*. Some of the beats of shorter QRS duration resemble in contour the premature systoles of Fig. 5, *A*, and, for that reason, are considered to be of ectopic origin.

Unlike the previous cases, in this case the QRS of the ectopic beat is not of normal duration, although it is not as long as the QRS of the dominant rhythm. To explain this, we must again localize the ectopic site of impulse formation to the interventricular septum below the bifurcation of the common bundle. The explanation would then be that the impulses are originating below the region of block, but that the spread to the two bundle branches is not equal in time, and because of this, the resultant QRS shows slight prolongation.

*This is part of a record previously reproduced in Katz: *Electrocardiography.* Philadelphia, 1941, Lea & Febiger, Fig. 394.

In Fig. 5, *B*, Lead I shows ectopic complexes of two varieties, one with an upright QRS like that of left bundle branch block, and the other with an inverted QRS which simulates right bundle branch block, indicating that here we are dealing with two foci of impulse formation below the bifurcation of the common bundle and below the region which gives rise to intraventricular block of the beats of supraventricular origin; one impulse spreads more rapidly to one bundle branch, and the other spreads more rapidly to the opposite bundle branch.

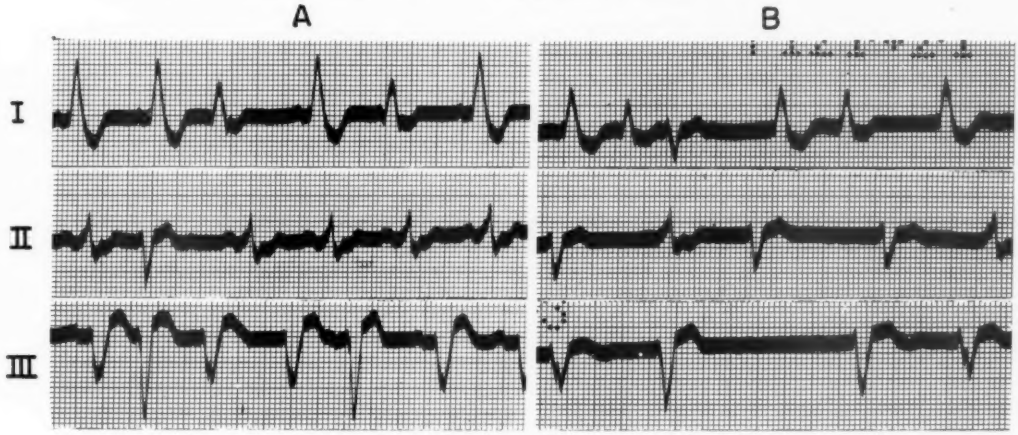

Fig. 5.—Case 3. Described and discussed in text.

That a supernormal phase of conduction is not involved in this record is proved by the second tracing, which shows the QRS of shorter duration both early and late in diastole, and shorter QRS complexes of two different types.

SUMMARY AND CONCLUSIONS

1. Three cases are presented in which ectopic beats of relatively normal contour and duration occurred during tracings of sinus rhythm with intraventricular block.

2. The explanations for these involved a consideration of (a) the site of ectopic impulse formation, and (b) the recovery phase of the region of bundle branch block.

3. The explanation offered by others,[1, 3] namely, an ectopic pacemaker situated in the interventricular septum, with equal spread to both ventricles below the region of block, is applicable in all three of our cases; however, as pointed out in one case (Case 1), the possibility of a supernormal phase in the area of bundle branch block must be considered.

4. In cases of sinus rhythm without intraventricular block, an ectopic pacemaker located in the septum may give rise to premature beats with a normal QRS duration, imitating nodal premature beats.

5. In Case 1 there was, in addition, another unusual arrhythmia, namely, a bigeminal rhythm which was interpreted as due to the fact

that every second beat was a premature beat originating in the S-A node, or, alternatively, as an instance of alternation of S-A conduction.

We are indebted to Dr. L. N. Katz for his valuable advice in this study.

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THE EFFECT ON THE PLASMA VOLUME OF DEHYDRATION PRODUCED BY A LOW-SALT DIET AND AMMONIUM CHLORIDE

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IT HAS been accepted[1, 2] that the plasma volume remains relatively constant with dehydration because it is protected by the much larger extracellular fluid volume. With the use of improved techniques, however, it has been found that the plasma volume is not constant, but shows considerable fluctuation. It has been demonstrated in animal experiments that the plasma, as well as the interstitial fluid, contributes to the water lost in dehydration induced by the removal of gastrointestinal secretions[3] or by the intraperitoneal injection of glucose.[4] In the early stages of diabetic acidosis,[5] the plasma volume decreases before significant dehydration develops. In cardiac edema, where there is a great excess of interstitial fluid, the plasma volume is not constant, but will show a considerable decrease after diuresis, even though edema persists.[6, 7]

The mechanism of the action of ammonium chloride has been well established as a result of carefully controlled balance studies on normal and abnormal subjects.[8] In general, these persons were on fixed diets, usually low in sodium chloride and limited in fluid intake. Considerable variation is noted in the diuretic effect of ammonium chloride on the normal subjects, as reported in the literature; this is due, in part, to the use of different doses of the drug and to variations in the duration of the observation period. The diuresis varied from none[8b] to 2.5 kilograms, or 3.6 per cent of the body weight.[8c] Little information is available concerning the change in plasma volume, even as judged by changes in concentration of serum proteins or hematocrit values.

Since ammonium chloride is a frequently used diuretic, it would appear helpful to know how much diuresis it produces in normal persons in order to evaluate the diuretic response of patients. The studies in the literature are not closely comparable to the usual hospital method of employing ammonium chloride as a diuretic because the subjects had been on a fixed regimen for some days before the administration of the drug.

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TABLE I

THE PERCENTAGE CHANGE IN PLASMA VOLUME, HEMATOCRIT VALUE, SERUM PROTEIN CONCENTRATION, AND BODY WEIGHT AFTER THE CONTINUOUS ADMINISTRATION OF 9 GM. OF AMMONIUM CHLORIDE DAILY

SUBJECT	DAYS ON 9 GM. OF AMMONIUM CHLORIDE	PERCENTAGE CHANGE IN PLASMA VOLUME	PERCENTAGE CHANGE IN CONCENTRATION OF SERUM PROTEIN	PERCENTAGE CHANGE IN HEMATOCRIT VALUE	PERCENTAGE CHANGE IN TOTAL BLOOD VOLUME	PERCENTAGE CHANGE IN BODY WEIGHT	ACTUAL CHANGE IN PLASMA CARBON DIOXIDE COMBINING POWER IN VOLUME PER 100 C.C.
1	3	−10.8	----	0	−10.7	−6.1	−18.0
2	3	− 8.1	+ 7.3	+ 1.8	− 6.6	−4.7	−11.2
12	3	− 9.3	----	+ 2.8	− 5.0	−4.2	----
13	3	−13.8	----	+ 3.7	− 9.0	−2.4	----
3	4	−13.7	----	−10.5	−15.3	−5.8	− 8.0
4	4	−14.1	+ 5.3	+ 1.1	−13.3	−5.1	− 6.7
5	4	−31.0	+ 6.5	+18.5	−19.3	−7.6	----
6	4	−12.5	+11.2	− 3.6	−12.4	−3.3	0
14	4	−20.0	----	+ 3.3	−11.8	−4.9	----
15	4	− 4.2	− 8.0	+ 2.2	− 2.5	−0.1	----
Average 3-4		−13.75	+ 6.5	+ 1.9	−10.6	−4.4	----
7	6	−24.4	+27.6	− 7.4	−25.1	−4.4	----
8	6	----	+15.7	----	----	−2.9	----
9	6	− 4.9	+ 7.5	----	− 5.6	−2.8	−12.2
10	6	− 6.8	+14.2	− 6.7	−11.7	−2.6	− 0.2
11	7	−23.0	----	0	−16.0	−1.3	− 1.0
5	8	−18.6	− 3.7	+15.5	− 7.2	−9.3	----
6	9	− 7.1	− 1.9	− 8.1	− 9.1	−3.5	− 4.0
9	10	+ 4.9	+ 6.2	+ 3.0	+ 5.6	−3.5	−21.8
10	10	+ 0.6	+ 2.9	− 8.7	− 6.7	−3.0	−23.6
8	13	− 4.4	+ 6.1	− 7.9	− 9.2	−3.6	----
11	15	−16.7	----	− 7.0	−15.2	−1.8	−19.0
6	16	−14.3	+ 1.8	− 7.0	−16.3	−3.6	− 1.0
9	16	−11.6	+10.0	+ 3.0	−11.1	−5.1	−25.4
10	16	− 1.3	0	− 4.1	− 4.9	−3.6	−19.8
8	19	− 2.3	+ 8.4	− 9.8	− 8.3	−4.3	----

In an effort to evaluate the response of normal subjects to a low-salt diet and ammonium chloride, and to further study the effects of dehydration on the plasma volume, the following observations were made.

METHODS

Fifteen hospital patients without evidence of cardiovascular or renal disease, who had never had edema and who were not ill at the time of the observations, were selected as normal subjects for study. Each patient had been on the routine hospital diet for several days before the observations were started. The subject was carefully weighed on a beam balance, accurate to 2 grams, in the postabsorptive state, on the morning of the observations. After the weighing he was placed on a comfortable stretcher and blood samples were taken for the determination of the plasma volume,[9] hematocrit value, serum proteins,[10] and, in some cases, CO_2 combining power.[11] After the initial observations were made, the subject was kept at rest in bed on a diet low in salt (about 2.5 Gm.), with 70 Gm. of protein, and the caloric content of the diet was adjusted to 40 per cent above the estimated basal caloric consumption. Fluids were permitted ad libitum. As far as could be ascertained, the diet was consumed completely, so that it can be assumed that changes in weight closely reflected changes in the water content of the body. At the start of this diet, 3 Gm. of ammonium chloride in 0.5 Gm., enteric-coated tablets were taken with each meal, so that 9 Gm. of ammonium chloride were ingested daily.

In the postabsorptive, rested state, the plasma volume of the normal subject is remarkably constant. In this laboratory the estimation of plasma volume was repeated fourteen times on successive mornings on twelve normal subjects in the rested, postabsorptive state, and showed an average variation of plus 0.88 per cent; the greatest variations, in one instance each, were plus 6 and minus 5 per cent. These results are in accord with those of others.[12, 13]

RESULTS

The observations on the majority of the subjects were completed after three or four days on ammonium chloride, chiefly because either they were no longer available for study or an adequate diuresis was produced. The alterations in total blood volume, plasma volume, hematocrit value, serum protein, and weight, expressed as percentage change from the initial determinations, are given in Table I. Plasma volume varies considerably with the size of the body, so that changes in the plasma volume of a group of persons of different size cannot be directly compared.

Ten subjects who received the drug for three or four days experienced an average diuresis of 4.4 per cent of their body weight, with a fall in plasma volume of 13.8 per cent. The hematocrit and serum protein values increased, although these changes were considerably less than the change in plasma volume, and failed to reflect accurately the fall in plasma volume. The actual change in plasma volume in these people averaged 436 c.c., with an average weight loss of 3 kilograms. The decrease in plasma volume accounted for 12.2 ± 1.2 per cent of the

total weight lost. The greatest change was noticed in Case 5, i.e., a decrease in plasma volume of 1,120 c.c. and a 4.6 kilogram weight loss.

Six subjects who received ammonium chloride for six to eight days showed a considerably greater variation in response which was in part the result of the selection of the cases. Some subjects who did not show an adequate diuresis after three or four days were allowed to continue the drug for a longer period before the observations were repeated.

Subsequent observations after nine to nineteen days on ammonium chloride indicated that the plasma volume was in part restored after its initial fall, in spite of the continued loss of water from the body as judged by the progressive weight loss. These fluctuations in the plasma volume are recorded in Table II.

TABLE II

THE PERCENTAGE CHANGE IN PLASMA VOLUME, HEMATOCRIT VALUE, SERUM PROTEIN CONCENTRATION, AND BODY WEIGHT AFTER THE CONTINUOUS ADMINISTRATION OF 9 GM. OF AMMONIUM CHLORIDE DAILY

SUBJECT	DAYS ON 9 GM. OF AMMONIUM CHLORIDE	PERCENTAGE CHANGE IN PLASMA VOLUME	PERCENTAGE CHANGE IN CONCENTRATION OF SERUM PROTEIN	PERCENTAGE CHANGE IN HEMATOCRIT VALUE	PERCENTAGE CHANGE IN BODY WEIGHT
5	4	−31.0	+ 6.5	+18.5	−7.6
	8	−18.6	− 3.7	+15.5	−9.3
6	4	−12.5	+11.2	− 3.6	−3.3
	9	− 7.1	− 1.9	− 7.1	−3.5
	16	−14.3	+ 1.8	− 7.0	−3.6
8	6	----	+15.7	----	−2.9
	13	− 4.4	+ 6.1	− 7.9	−3.6
	19	− 2.3	+ 8.4	− 9.8	−4.3
9	6	− 4.9	+ 7.5	----	−2.8
	10	+ 4.9	+ 6.2	+ 3.0	−3.5
	16	−11.6	+10.0	+ 3.0	−5.1
10	6	− 6.8	+14.2	− 6.7	−2.6
	10	+ 0.6	+ 2.9	− 8.7	−3.0
	16	− 1.3	0	− 4.1	−3.6
11	7	−23.1	----	0	−1.3
	15	−16.7	----	− 7.0	−1.8

Of considerable interest was the actual weight lost by these patients who had no suggestion of edema. The average weight loss of the group of fifteen subjects after receiving the diet and ammonium chloride for three to seven days was 2.47 kilograms. Continuation of the drug over a longer period was associated with a continued loss of weight, although the changes were quite small.

DISCUSSION

It is apparent from the results of these studies that the plasma volume shares in the dehydration induced by ammonium chloride. It is, of course, true that the majority of the water lost was derived from the reservoirs other than the plasma volume, but in certain instances there was a profound reduction of plasma volume.

Since sodium and potassium balance studies were not carried out on these subjects, it is not known whether the majority of the water lost under these circumstances came from the interstitial fluid or from the cells. However, others[8] have found that both sodium and potassium are lost in the urine, which suggests that the lost water must come from both the extracellular and intracellular fluid compartments. Gamble indicated that at first the water loss comes largely from the extracellular fluid and later the intracellular fluid.

The fluctuations in plasma volume after the initial fall continued in spite of progressive loss of body water. In general, these subsequent changes were toward a restoration of the plasma volume, and suggest that considerable shifts of water must occur within the body as diuresis continues, presumably because of removal of water from the cells or from extracellular fluid that is not readily mobilized. Judging from the observations of others,[3, 4, 8] who have found that a considerable amount of potassium is lost in the urine, it would appear that the plasma volume was made up by shift of water from the cells.

There was only a directional relationship in these cases between the intensity of the diuresis and the fall in plasma volume. Some cases, in which the diuresis was large with a relatively small decrease in the plasma volume, would suggest that the plasma volume was well protected by the extracellular fluid. In others, however, the large decrease in plasma volume with little change in weight suggested that there was very little protection of the plasma volume. As far as we could ascertain, all subjects were well hydrated and had been on the same hospital regimen for several days before the observations were made.

The diuresis experienced by some of these subjects was greater than that reported in the literature. These observations, however, represent the response of "normal" subjects who had been on the usual hospital regimen, with salt and water ad libitum, to the low-salt diet, as well as to large doses of ammonium chloride, over a three- to seven-day period. In general, in the cases previously reported,[8] the subjects were on a diet limited in salt and fixed in its constituents for some days before the administration of the drug. Loeb, et al.,[8e] however, noted no difference in the loss of potassium, sodium, magnesium, or calcium with the administration of ammonium chloride in the case of their carefully studied normal subject when he was on a "salt poor" diet and on the same diet with an additional 120 milliequivalents of sodium chloride.

These results suggest that it is not uncommon for a normal, hospitalized patient to have a diuresis of 2 to 4 kilograms on a low-salt diet and 9 Gm. of ammonium chloride per day. Such a diuresis in patients suspected of having edema has often been incorrectly interpreted as evidence of edema, but it represents only the response of a normally hydrated person to the diuretic regimen.

A comparison between the percentage change in plasma volume and the percentage change in hematocrit values and the concentration of

serum proteins shows a considerable discrepancy. Certainly, the changes in hematocrit values completely failed to express the changes in the plasma volume. This can in part be explained by the fact that determinations of the plasma volume require from 50 to 80 c.c. of blood, and, therefore, the loss of erythrocytes which may be expected from repeated determinations would produce a lower hematocrit value. It does not adequately explain the changes noted with the second plasma volume determination, for it seems unlikely that the removal of only 50 c.c. of blood three or four days previously would suffice to produce this loss of erythrocytes. The inability to accurately measure changes in plasma volume by changes in the hematocrit value has been demonstrated before by Ebert and Stead.[14, 15] They have indicated that shifts of blood from the larger to the smaller vessels may produce such changes in the hematocrit value without alterations in the number of erythrocytes in the circulation.

The changes in the concentration of serum proteins were consistently less than the changes in plasma volume, although in the same direction. As with the hematocrit, the changes in the concentration of serum proteins failed to express the extent of the dehydration of the plasma. This has been noted by others,[3, 16, 17] and suggests that a change in the concentration of serum proteins as an index of the change in plasma volume is not reliable. A change in the concentration of serum proteins may indicate only a directional shift in the plasma volume, but not a quantitative change, for the change in plasma volume is generally greater than the change in serum protein concentration. The failure of the serum proteins to follow more closely the changes in plasma volume is in accord with the concept of Madden and Whipple[18] that the serum protein is in a state of "dynamic equilibrium." It suggests that a decrease in the volume of the plasma induced over several days may be associated with decreases in the total amount of protein in the plasma.

CONCLUSIONS

1. Dehydration induced in man by the use of a low-salt diet and 9 Gm. of ammonium chloride daily is associated with a decrease in the plasma volume and a smaller rise in serum proteins and hematocrit values.

2. The amount of water loss varied considerably, but, in general, amounted to 3 or 4 per cent of body weight.

3. Only a directional relationship existed between the decrease in the plasma volume and the amount of diuresis.

4. The difference in the concentration of serum proteins or hematocrit values failed to reflect quantitatively the changes in the plasma volume.

5. Continued administration of ammonium chloride was accompanied by a secondary rise in plasma volume toward the control level, with subsequent fluctuations, although diuresis persisted.

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THE CIRCULATION IN MAN IN CERTAIN POSTURES BEFORE AND AFTER EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

I. Physiologic Aspects*

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THE effect of posture on the circulation has long been a subject of interest to many students of vascular physiology. This subject has assumed increasing significance since the syndromes of spontaneous and of postoperative orthostatic hypotension have been recognized clinically. The relatively recent introduction of extensive sympathectomy for the relief of essential hypertension has resulted in opportunities for seeing and studying certain persons who have orthostatic hypotension and orthostatic tachycardia after this type of operation. Thus, information relative to the dynamics of the circulation which formerly had to come solely from studies on animals can now be obtained from studies on man.

HISTORICAL REVIEW

A good résumé of the historical aspects of the operation of sympathectomy for hypertension may be found in an article by Adson, Craig, and Brown.[1] Roth made perhaps the first extensive study of the effects of posture on the blood pressure and pulse rate after sympathectomy. She noted that no significant orthostatic decreases in blood pressure were produced by operations which did not produce extensive abdominal sympathetic denervation.

Allen and Adson[2, 3] have reported on the physiologic effects of extensive sympathectomy[1] on essential hypertension. More recently, Adams and his co-workers[4] studied the effects of extensive sympathectomy on the cardiorenal system. They found that the pulse rate and cardiac output were reduced after sympathectomy.

PURPOSE, SCOPE OF STUDY, AND DEFINITIONS

The purpose of the present investigation was to study, by as many approaches as were practicable under controlled conditions, the physiologic effects of sympathectomy and its effect with change of body

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posture. Accordingly, we studied the effect of the horizontal and the 60-degree head-up postures on (1) pulse rate, (2) blood pressure, (3) pulse pressure, (4) differential blood pressure, (5) response to the Flack test, and (6) cardiac output before and after extensive sympathectomy in ten cases of essential hypertension (Cases 1 to 10 of this and the succeeding report). In addition, the circulation time and the response to the cold-pressor test were studied while the patients were in the 60-degree head-up posture, and the volume of the leg while they were standing erect. Further studies were done on the same persons in an effort to modify orthostatic vascular responses; these studies will be reported in a subsequent paper. The word "orthostatic" is used in this report to refer to the 60-degree head-up posture, as well as to the erect or standing posture, although, strictly speaking, the term refers to the latter only.

It was deemed more advisable as well as more practicable to study a small number of cases from many aspects rather than a larger number less thoroughly and extensively. We realize the hazards of attempting to interpret percentages based on such small groups of cases. This becomes all the more obvious when the marked lability of the various factors which comprise the total picture of the circulation, particularly in cases of hypertension, is recalled.

Experience has shown that, in the early days of convalescence after extensive splanchnic sympathectomy for hypertension, the average patient cannot tolerate the upright posture long without syncope. The 60-degree head-up posture, therefore, was selected for most of the studies which were made, since it was felt that most patients could tolerate this posture. We are fully aware that use of the 90-degree head-up posture would have given a more accurate picture of the total effect of gravity on the circulation. We believe, however, that the differences in circulatory reaction which occur between the 60- and 90-degree head-up postures are largely quantitative. The 90-degree, or erect, posture has its disadvantages also, for certain muscular movements and muscular tension would be superimposed, which would make it more difficult to evaluate the role of gravity. We were more interested in knowing the trend of reactions.

PATIENTS STUDIED AND PROCEDURE

Seven of the patients were men and three were women. Their ages ranged from 25 to 57 years; the average age was 39.6 years. Seven patients had hypertension, Group 2, and three, hypertension, Group 3, according to the classification of essential hypertension by Keith, Wagener, and Barker.[5] All underwent bilateral, subdiaphragmatic, retroperitoneal, intra-abdominal resection of the splanchnic nerves, celiac ganglia, and upper two lumbar sympathetic ganglia and intervening trunks. In addition, the ninth, tenth, and eleventh thoracic sympathetic ganglia and intervening trunks were resected in two of the cases. Preoperative studies were made about four days after the patients were admitted to the hospital. Postoperative studies were done, on the average, twelve days after the second stage of sympathectomy. The patients had been walking for about five days prior to the postoperative studies.

All determinations except cardiac output were made at one session in an air-conditioned room in which the relative humidity was 40 per cent and the temperature ranged from 78 to 82° F. Studies of cardiac

output were made on the next day. A tilt table was used which permitted observations while the patients lay on the table in the horizontal and in the 60-degree head-up postures. Ordinary blood pressure cuffs were used on one arm and on both thighs just above the knees. The cuffs on the thighs were reinforced by towels fastened snugly with pins. For measurements of blood pressure in the thighs, Tycos aneroid sphygmomanometers which had been checked for accuracy against a mercury manometer were used. The cuffs were 12 cm. in width. Judging from studies by Wiggers,[6] a cuff that wide should give fairly accurate readings. A Bowles stethoscope was used, and the diastolic pressure was noted at the level at which auscultatory sounds were suddenly muffled. Patients rested on the table for at least twenty minutes before any studies were begun. In general, three determinations of blood pressure and pulse rate were made at intervals of two minutes in each of the two body postures.

PULSE RATE

The pulse rates of all patients in the horizontal posture were higher after operation than before operation; the average postoperative increase was 13 beats per minute. The pulse rate while the patients were in the 60-degree head-up posture averaged 21 beats more after sympathectomy. The rate of acceleration of the pulse was studied by counting the pulse at intervals of fifteen, thirty, sixty, and 120 seconds after the patient was moved to the 60-degree head-up posture. After this, the patient was returned to the horizontal posture and the pulse rate was again counted after fifteen seconds. The results are shown in Fig. 1. Thus, the pulse rate was not only higher, but had a tendency to accelerate continuously after operation, in contrast to the tendency preoperatively to attain a fairly constant level after the patient had been in the head-up posture for thirty seconds.

Roth[7] noted in a study of twelve cases of essential hypertension that active assumption of the erect posture, which is not entirely comparable with this study, resulted in an average increase of 12 beats per minute prior to sympathectomy and an average increase of 32.9 beats per minute subsequent to sympathectomy. Adams and his co-workers, on the contrary, found a slight decrease in heart rate when subjects were in the horizontal posture after sympathectomy.

The exact reason for the invariably faster pulse rate in both postures which was found in our series of cases after sympathectomy is not known. We doubt whether the Bainbridge reflex has much to do with it, for a tight abdominal binder, which should increase venous return to the right auricle and perhaps increase venous pressure within the right auricle (that is, activate the Bainbridge reflex), actually slows the heart. When patients are in the head-up posture after sympathectomy, the blood pressure may fall to rather low levels and evidences of impending syncope may appear. Reduction of pressure in the right auricle would be expected under these circumstances; yet, the pulse rate actually accelerated. It may be that, in such persons, vasomotor

reflexes which originate from pressure changes within the thoracic aorta and within the carotid sinuses exert a greater role in the regulation of blood pressure and pulse rate than vasomotor reflexes which arise from pressure changes within the right auricle. The former reflexes, too, may be activated more readily than the latter. Such an arrangement seems not only reasonable but desirable for the organism, since it would afford a quicker and a more direct control of the circulation, particularly for such vital structures as the brain, by counteracting sudden or harmful decreases or increases in blood pressure.

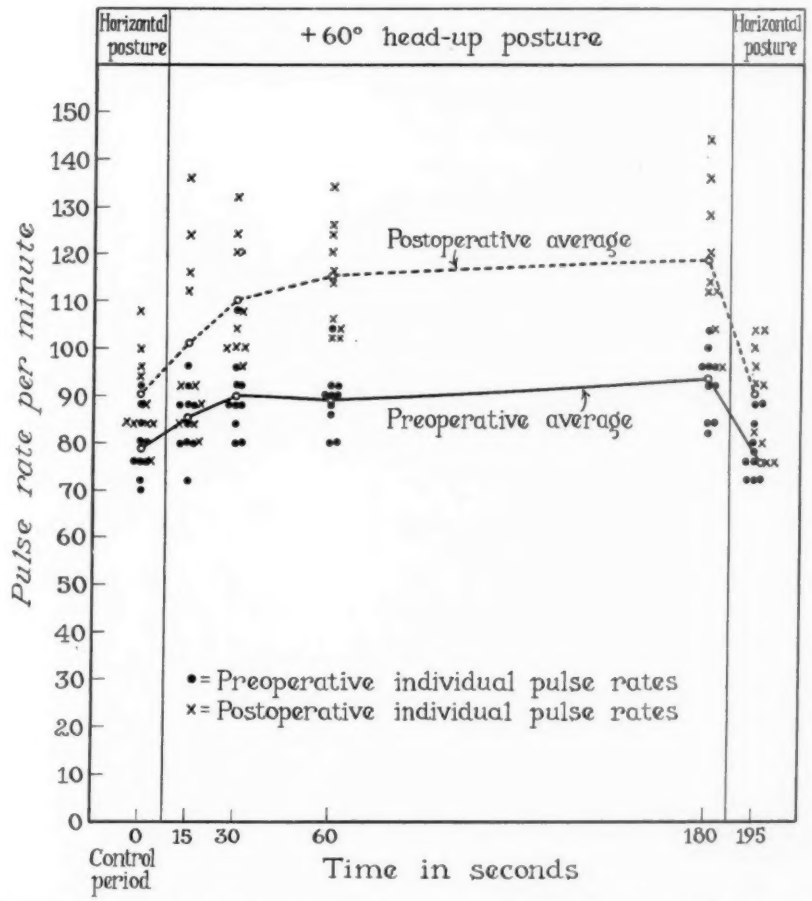

Fig. 1.—Preoperative and postoperative pulse rate in horizontal posture and at increasing time intervals after passive tilt to 60-degree head-up posture.

According to this concept, the increased pulse rate after sympathectomy could be due to a reduction in the number of pressoreceptive stimuli originating within the thoracic aorta and within the carotid sinuses as a result of a decrease in intra-aortic and intracarotid blood pressures secondary to a general decrease in peripheral resistance.

BLOOD PRESSURE

The consensus[8] as to the so-called normal response of the blood pressure when subjects are moved from the horizontal to the erect posture is that the systolic pressure does not change materially, whereas the diastolic pressure usually rises; many workers have reported a rise of 8 to 10 mm. of mercury in the diastolic pressure. In a recent study of 112 persons who had essentially normal blood pressure, one of us (Gambill[9]) found the systolic pressure unchanged, while the diastolic pressure rose an average of 6 mm. of mercury after subjects had stood for a period of three minutes.

The present study of blood pressure in the horizontal posture revealed that sympathectomy was followed by an average decrease of 21 mm. in systolic, and an increase of 7 mm. in diastolic, pressure. Study of the blood pressure in the 60-degree head-up posture before and after operation revealed that operation resulted in an average decrease of 36 mm. in the systolic, and 21 mm. in the diastolic, pressure (Fig. 2). When patients were moved on the tilt table from the horizontal to the head-up posture after operation, the systolic pressure decreased an average of twice as much, and the diastolic pressure, seven times as much, as before operation. Even in cases of marked orthostatic hypotension and tachycardia, vascular adjustments on return of the patient to the horizontal posture were rapid. For example, after one patient (Case 1) had been in the 40-degree head-up posture for seven minutes, the systolic pressure at the time of this study was 62, and the pulse rate was 132 per minute. Within twenty seconds after he was returned to the horizontal posture the systolic pressure was 116 and the pulse rate had decreased from 132 to 76.

Allen and Adson[3] stated that orthostatic hypotension and tachycardia definitely disappear a variable time after sympathectomy. The mechanism involved in the change is not known.

DIFFERENTIAL BLOOD PRESSURE

By differential blood pressure is meant the difference in blood pressure between the thigh and the arm. Careful studies in recent years, particularly those of Strang,[10] Bazett,[11] Hamilton and co-workers,[12] Cady,[13] and one of us (Gambill[9]), leave little doubt that a difference exists in the blood pressure in the thigh and arm of persons with normal pressure. Cady studied the differential blood pressure in seventy-five cases of hypertension and in seventy-five cases of normal pressure. He found that extensive sympathectomy reduced the difference in blood pressure in the thigh and arm. His conclusion was that this difference in pressure is due to differences in peripheral resistance in the leg and arm, and that any procedure which tends to equalize the resistance in the arteries of the two limbs also tends to equalize the pressures within these vessels. Conversely, unequal variations in

the resistance of the arteries of the leg and arm would affect the differential pressure. Bazett[11] postulated that the difference in blood pressure in the leg and arm was due to the greater transmission of kinetic energy into pressure energy in the leg than in the arm.

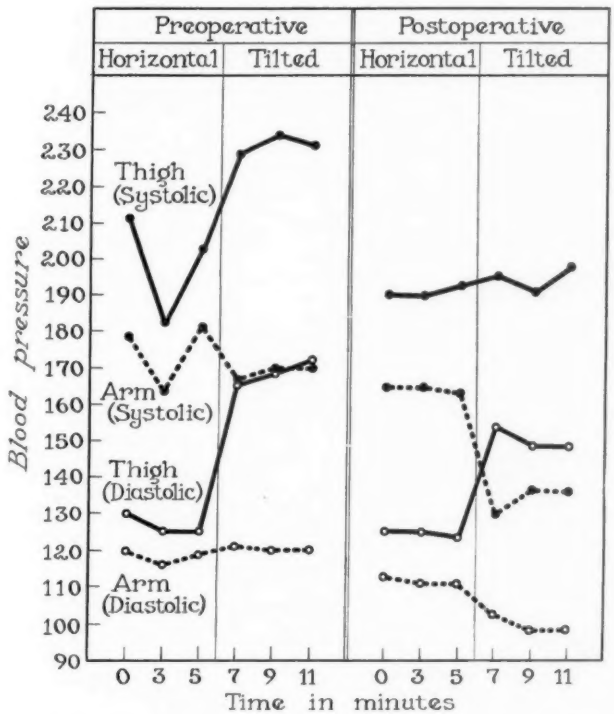

Fig. 2.—Mean blood pressures in arm and thigh in ten cases in horizontal and tilted (60-degree head-up) postures before and after sympathectomy.

The differential blood pressure in the present investigations was calculated from measurements of blood pressure from the arm and leg according to the procedure outlined. Contrary to expectations, sympathectomy actually resulted in an average increase of 8 mm. in both the systolic and diastolic differential pressures when the patients were in the horizontal posture. In the head-up posture after sympathectomy, reductions in systolic pressure were the same in the arm and leg, but reductions in the diastolic pressures were slightly greater in the leg. A greater reduction of blood pressure might be expected in the leg than in the arm if only the theoretical effect of sympathectomy on the reactivity of the vessels in the sympathectomized limb were considered. Such a result does not necessarily occur because peripheral resistance is only one of several elements which determine the level of blood pressure; cardiac output and circulating blood volume are among other factors which also may affect it. The fact that the diastolic blood pressure in the arm decreased after sympathectomy when patients were

placed in the head-up posture stresses the role of factors other than local vascular reactivity in determining blood pressure levels, for the arm vessels were not sympathectomized.

PULSE PRESSURE

Schneider and Truesdell,[14] after studying the postural reactions of a large number of healthy persons, concluded that the product of pulse rate and pulse pressure was unchanged with change of posture. It has been stated[15] that a pulse pressure of less than 30 or more than 50 mm. Hg is abnormal. Sewall[16] concluded, after a study of several hundred persons, that the pulse pressure always decreases when a change is made from the recumbent to the erect body posture. This decrease usually is the result of the decline in systolic and the rise in diastolic pressure which occurs on assumption of the upright posture.

The purpose of the present study was to observe what effect sympathectomy has on pulse pressures in the arm and leg when the patients were in the horizontal and in the 60-degree head-up postures.

The average pulse pressure in the arm when the patients were in the horizontal posture decreased 16 mm., and that in the leg decreased 12 mm., after sympathectomy. After sympathectomy, when the patients had remained for one minute in the 60-degree head-up posture, the average decrease in pulse pressure was 21 mm. in the arm and 24 mm. in the leg. The greatest decrease in pulse pressure after operation occurred in those cases in which hypotension was greatest in the head-up posture (Fig. 3). Although both systolic and diastolic pressures decreased when patients were placed in the head-up posture after operation, the lowered pulse pressure was predominantly the result of a greater decrease in the systolic than in the diastolic pressure.

Response to Flack Test.—The work of Grimes[17] and MacLean and Allen[18] has emphasized the possible significance of the Flack test in physiology and in clinical medicine. As a result of a study of 1,000 subjects in twenty years, Grimes considered a systolic rebound of 25 mm. Hg or less as a normal response to this test, and a rebound of more than 25 mm. Hg as an abnormal response.

It was felt that a study of the influence of certain postures on the Flack test before and after extensive sympathectomy might throw some light on the role of venous return to the heart in the regulation of the circulation, particularly since considerable orthostatic hypotension is likely to develop after sympathectomy. The test as used in the present study was as follows: The patient blew against the column of mercury in the sphygmomanometer until it attained a height of 20 mm., and maintained it at that level for twenty seconds. The blood pressure in the arm was measured during the last ten seconds of this period, after which the pressure within the arm cuff was quickly raised to a point higher than the previous control systolic level. After cessation

of blowing, the cuff was deflated rapidly until the first systolic sound was heard. This sound was designated as the level of the rebound pressure. In most instances the test was performed twice, and the average of the two rebound pressures was calculated. This test was done while patients were in the horizontal posture and again after they had been in the 60-degree head-up posture for two minutes. The term "rebound" denotes the number of millimeters of increase or decrease, respectively, in the systolic blood pressure above or below the level of the control blood pressure.

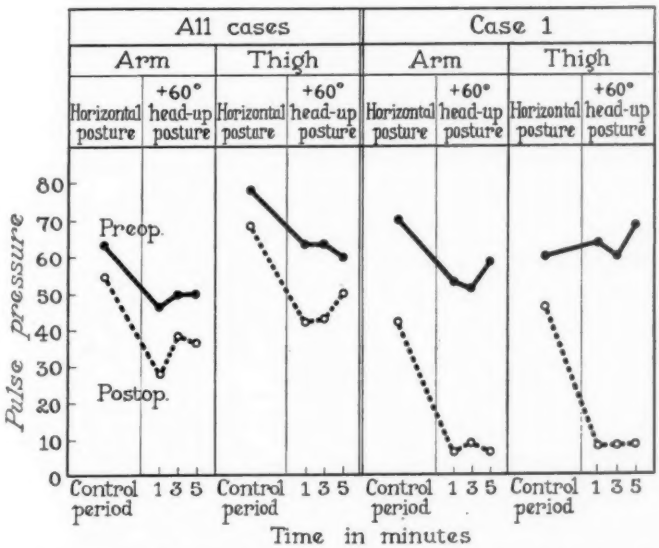

Fig. 3.—Comparison of average pulse pressures in arm and thigh in all ten cases with those in Case 1. Severe orthostatic hypotension and tachycardia developed in Case 1 after operation.

Prior to operation, the Flack test resulted in a decrease in systolic blood pressure in both postures; the greatest decrease occurred when patients were in the head-up posture. The diastolic pressure during the Flack test increased when the patients were in the horizontal posture but decreased when they were in the head-up posture. The systolic rebound pressure averaged 15 mm. more when the patients were in the horizontal posture than when they were in the head-up posture. After sympathectomy, when the patients were recumbent, the test resulted in eight times more reduction in systolic blood pressure than before operation. Whereas the diastolic pressure increased an average of 46 mm. during the Flack test in the horizontal posture before operation, it decreased in every instance when the test was similarly performed after operation. The systolic rebound pressure when the patient was in the horizontal posture was only two-thirds as great after as before operation. After operation, the response to the Flack test in

the head-up posture was strikingly impaired. In fact, the blood pressure during the period of blowing fell so low as to be obtainable in only three of nine cases studied. Whereas before operation the systolic rebound pressure in the head-up posture was 25 mm. more than the control value, after sympathectomy it was only 9 mm. more than the control pressure (Fig. 4). As expected, the lowest systolic rebound pressure occurred among patients who exhibited postoperative orthostatic hypotension and tachycardia. For example, in Case 1, as mentioned previously, orthostatic hypotension and tachycardia developed after sympathectomy, and, during the Flack test, syncope and a short convulsive seizure developed. One or two other patients had mild syncope during the Flack test.

It seemed desirable to see whether α-N-dimethyl-*p*-hydroxyphenethylamine sulfate (paredrinol sulfate) would improve the reactions to the Flack test. Accordingly, 20 mg. of this drug were given subcutaneously, and then the response to the Flack test was noted while the patient was in the horizontal posture. This was tried in Case 8 fifteen days after the second stage of sympathectomy and after control values for the Flack test had been ascertained. Only a slight improvement was noted in the response to this test after the administration of paredrinol sulfate. This patient had been walking around for a few days prior to the test, and had probably recovered a considerable degree of reactivity in the sympathectomized vessels—enough perhaps to counteract the effects of an increase of 20 mm. Hg in intrathoracic pressure while in the horizontal posture.

The exactness of the information revealed by the Flack test may be open to question, but the changes are so striking that their significance cannot be doubted. It is not assumed that the rebound pressures, as obtained, are absolutely accurate, for it is possible that the blood pressure may not have been obtained at its highest point. The fact that the pressure rebounded to the levels mentioned seems important.

Grimes felt that, other things being constant, the height of the rebound blood pressure varies inversely as the elasticity of the arteries. The general decrease in rebound pressure after sympathectomy in the present studies agrees with this view, for sympathectomized vessels have lessened constrictor tone, which makes them more distensible and reduces their elastic recoil. It has been stated that the pressure within a vein results (1) from the residuum of pressure created by cardiac systole, (2) from the degree of tonus in the vessels, which, in turn, is influenced by the vasomotor nervous system, and (3) from hydrostatic pressure. To these influences must be added the influence of muscular action with its milking effect on the veins. It is easy to reason, then, that sympathectomy, by decreasing the effect of at least the second and fourth factors, might decrease the venous pressure gradient from legs and abdomen to the thorax. Cardiac filling, there-

fore, could be impaired by relatively smaller increases in intrathoracic pressure. In fact, MacLean and Allen have shown by roentgenologic means that there is a decrease in the size of the heart shadow in cases in which the Flack test results in much hypotension. When cardiac filling is sufficiently impaired by such a procedure, even an accelerated pulse rate and localized increases in peripheral vasoconstriction might not prevent a decrease in blood pressure. If, in addition, hydrostatic forces are brought into play by tilting the subject to the semierect

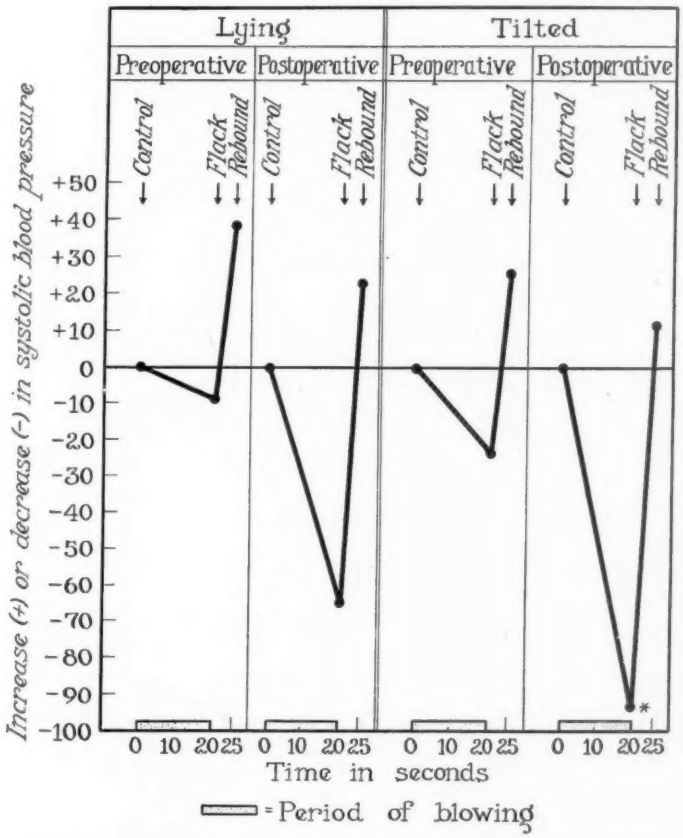

Fig. 4.—Flack test. Effect on systolic blood pressure of maintaining a column of mercury at 20 mm. for twenty seconds by blowing against it. The figure 94, as given for the depression in systolic pressure, may not be strictly accurate because it represents the average result for all cases, in some of which, pressures were too low to measure. In these cases the decrease in pressure on blowing, for purposes of calculation, were taken as equal to the control systolic pressure. Almost certainly the pressure did not fall to zero.

posture, these effects are augmented. Thus, a greater decrease in the systolic blood pressure resulted during the Flack test while the patients were in the head-up posture than while they were in the horizontal posture. Sympathectomy seemed to augment these effects further. MacLean and Allen showed that a nearly normal Flack test resulted when subjects were lying in a 30-degree head-down posture.

CIRCULATION TIME

The circulation time from arm to foot and foot to arm was measured before and after sympathectomy. We were interested in comparing the circulation time in cases of postoperative orthostatic hypotension with that in cases in which this condition did not develop, in an effort to obtain additional information concerning the mechanism of this phenomenon. Recent studies of the circulation time of sympathectomized patients have been made by Kvale and associates[19] and Smith and associates.[20]

The circulation time from arm to tongue, arm to foot, foot to tongue, foot to arm was studied in seven of the ten cases while the patients were in the 60-degree head-up posture, under the environmental conditions mentioned previously. The subjects had been without food from four to seven hours prior to the test, and had been lying on the tilt table for at least an hour before the test was done. Macasol* was used as the test solution; 2 c.c. were used for the arm-to-foot time and 3 c.c., for the foot-to-arm time. This was given intravenously by means of a 3 c.c. syringe and a 20-gauge needle. The solution was injected into the median antecubital vein in order to ascertain the arm-to-foot time, and into one of the dorsal veins of the foot for the foot-to-arm time. Thirty seconds elapsed after release of the tourniquet before the test solution was injected in the punctured vein. A stop watch was employed for measuring the circulation time. Ten minutes elapsed between the injections in the arm and foot.

In three cases the circulation time increased, and, in four, it decreased after sympathectomy (Fig. 5). Whereas a decrease in the arm-to-foot and arm-to-tongue circulation time occurred after sympathectomy in the group in which the postoperative reduction in blood pressure was minimal to fair, the circulation time was more than doubled in the group in which the reduction in blood pressure was good and orthostatic hypotension developed after operation. Apparently, orthostatic hypotension is associated with a general slowing of the circulation. This may be related to marked vasoconstriction in the unsympathectomized upper part of the body and to a decrease in cardiac output when such subjects assume the head-up posture. The critical level of hypotension, below which circulation time is increased, has not been ascertained.

We tried to measure the circulation time from foot to tongue and from foot to arm without success, apparently because of pooling or stagnation of the test solution in the injected limb. This was suggested by the fact that no reaction was felt in the tongue for as long as three minutes after injection of the solution in the vein in the foot so long as the patient remained in the head-up posture. However, a

*Macasol is a mixture of magnesium sulfate, magnesium gluconate, calcium sulfate, sodium chloride, and copper sulfate in sterile distilled water, and is manufactured by Nepera Chemical, Inc., Yonkers, New York.

definite reaction occurred in the tongue, and then in the arm, about eight and sixteen seconds, respectively, after the patient was returned to the horizontal posture. Moreover, if, before returning the patient to the horizontal posture, a blood pressure cuff was placed around the thigh of the injected limb and was inflated above the diastolic blood pressure level, no reaction was experienced in the tongue for as long as three minutes after return of the patient to the horizontal posture. A strong reaction in the tongue and arm followed within six to ten seconds after deflation of the cuff. This and burning in the foot, relieved by assumption of the horizontal posture, offer additional proof that there was stagnation of the test solution in the leg while the patients were in the head-up posture. These observations indicate the difficulty of measuring circulation time in the head-up posture.

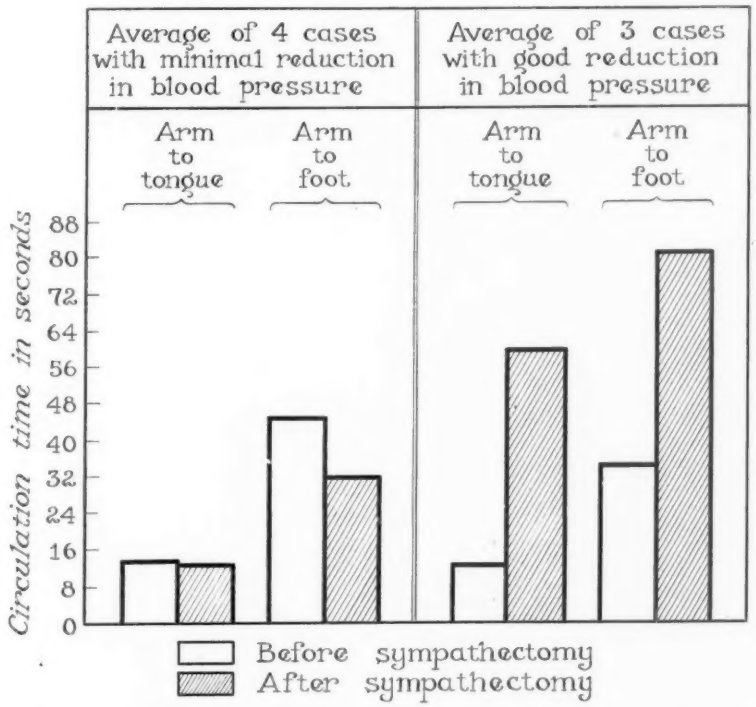

Fig. 5.—Average circulation time in seconds in 60-degree head-up posture before and after sympathectomy. Comparison of results obtained in four cases in which reduction of blood pressure was minimal with those in three cases in which reduction of blood pressure was good and considerable orthostatic hypotension and tachycardia followed sympathectomy.

RESPONSE TO COLD-PRESSOR TEST

Allen and Adson[2, 3] have observed that, in general, those patients who have good reductions in blood pressure as a result of sympathectomy tend to have the greatest diminution in blood pressure response to the cold-pressor test after sympathectomy, and vice versa.

The present study was done in an effort to learn more about the mechanism of the orthostatic hypotension which is so marked in some cases after sympathectomy. The test has been well established as a standard stimulus of blood pressure, and we felt that the results derived from it might also serve as a yardstick for comparison of the pressor effects of other agents which were employed during the investigations. The technique devised by one of us (Hines[21]) was used. The test was done while the patients were in the 60-degree head-up posture. They had been lying on a tilt table undergoing other studies for at least an hour before the test was done. They had been resting quietly on the table fifteen to twenty minutes prior to the test. Two minutes elapsed after the patient was placed in the head-up posture, and then a control blood pressure reading was taken, after which the test was performed.

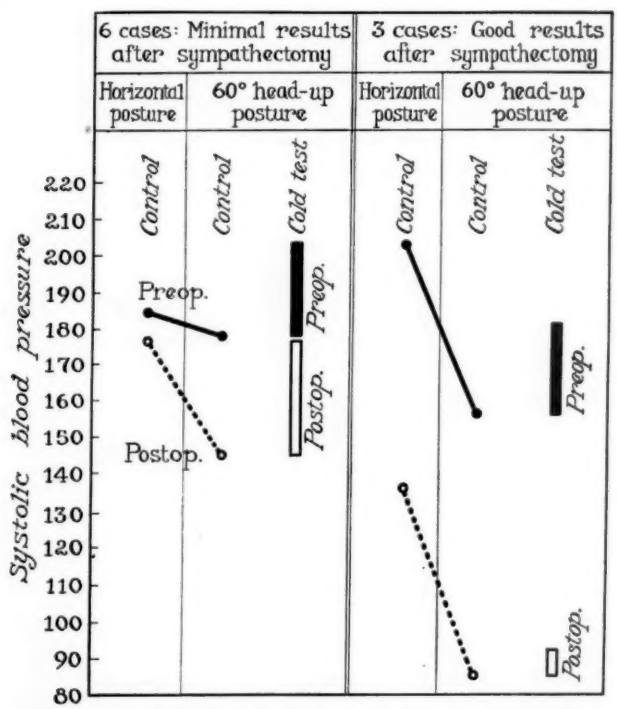

Fig. 6.—Effect of cold-pressor test with patients in 60-degree head-up posture. Comparison of cases in which reductions of blood pressure were minimal after sympathectomy versus cases in which reductions of blood pressure were good after sympathectomy.

As indicated in Fig. 6, in those cases in which the blood pressure was reduced considerably as a result of sympathectomy, the response to the cold-pressor test also was decreased by sympathectomy. On the other hand, patients who had little reduction in blood pressure postoperatively did not have a decreased response to the test. These results agree with those reported by Allen and Adson.[2, 3]

CARDIAC OUTPUT

All clinical evidence convinces the observer that marked degrees of orthostatic hypotension after sympathectomy must be associated with a reduction in cardiac output. The purpose of this study of cardiac output was to test that hypothesis. Certain investigators[22-24] have expressed the opinion that cardiac output changes little or not at all as a result of change in posture. However, most workers in this field[25-31] have noted significant decreases in cardiac output when the subjects stand erect. This was true of hypertensive, as well as normal, persons.

The cardiac output of five patients was measured in the horizontal and 60-degree head-up postures before and after sympathectomy. Two measurements were made on each patient in each position by the method described by Grollman. Basal metabolic rates were measured with the gasometer machine, using the open circuit method and the technique of Boothby and Sandiford.[32] Frequent determinations of blood pressure and pulse rate were made before and after each rebreathing test. Vital capacity was measured graphically by means of a spirometer.

The results are shown in Tables I and II. The variation between values obtained on the first and second tests were much greater for both postures after operation than they were before operation. The exact reasons for these differences are not clear, but we do not feel that they are related necessarily to technical error. It is more likely that they reflect the profound instability of the circulation which is obvious clinically so soon after sympathectomy. It would be interesting to repeat these observations several months after the operation, when the circulation has become readjusted and stabilized.

In four of the five cases, consumption of oxygen was decreased after sympathectomy. The basal metabolic rate was decreased in almost every instance after operation, and the average decrease was three times as much in the horizontal as in the head-up posture. The cardiac output was greater in both postures after sympathectomy; the greatest increase occurred when the patients were in the horizontal posture. Thus, in the horizontal posture, the cardiac output averaged 0.62 liter per square meter per minute more, and in the head-up posture 0.52 liter per square meter per minute more, after sympathectomy than it did before. However, a significant decrease in cardiac output occurred when the patients were moved from the horizontal to the head-up posture; the decrease averaged 0.56 liter per square meter per minute before operation and 0.66 liter per square meter per minute after operation. The stroke volume after operation was increased when the patients were in the horizontal posture, but was decreased after they were moved to the head-up posture. It was smaller in the head-up posture before, as well as after, the operation.

TABLE I

CARDIAC OUTPUT IN THE HORIZONTAL POSTURE

CASE	B.M.R. (PER CENT)	BLOOD PRESSURE (MM. HG)	PULSE RATE	O_2 CONSUMPTION (C.C. PER MIN.)	DIFFERENCE IN ARTERIAL AND VENOUS O_2 (C.C. PER L.)			CARDIAC OUTPUT (L. PER SQ. M. PER MIN.)			AVERAGE STROKE VOLUME (C.C. PER BEAT PER SQ. M.)
					TEST			TEST			
					1	2	AVERAGE	1	2	AVERAGE	
Preoperative											
1	- 1	165/96 166/104	74- 72	141	82.9		82.9		1.70	1.70	23.6
2*	+11	176/118 178/120	76- 80	248	63.4	68.5	65.9	2.10	2.20	2.19	26.9
3	+ 8	186/110 182/116	84- 84	257	59.6	56.1	57.8	2.32	2.46	2.39	28.4
4	+ 5	160/124 160/120	96-100	199	58.2	65.2	61.7	2.26	2.02	2.14	21.8
11†	+32	166/110 192/122	86- 90	240	48.5	57.8	53.1	3.39	2.84	3.11	25.7
Mean	+11	170/112 176/116	83- 85	217	62.5	61.9	64.3	2.52	2.24	2.28	25.3
Postoperative											
1	-16	126/ 88 124/ 92	72- 76	211	40.0	84.4	62.2	3.00	1.40	2.20	28.2
2	+ 2	140/ 98 156/108	84- 84	227	27.0		27.0	4.72		4.72	56.2
3	+ 6	178/118 184/116	86- 84	248	44.2	56.8	50.5	3.05	2.37	2.71	31.8
4	-11	144/112 146/114	88- 84	167	41.1	67.3	54.2	2.87	1.63	2.15	25.4
11†	0	166/116 184/116	80-100	175	54.5	40.1	47.3	2.29	3.12	2.70	33.7
Mean	-5.4	151/106 159/109	83- 86	206	41.4	62.1	48.2	3.15	2.12	2.90	35.1

*The patient was somewhat uncomfortable during the preoperative studies because of thoracic pain on the left side.

†Case 11 is not included in the series of ten cases mentioned at the beginning of this report. In this case, studies were limited to measurements of cardiac output.

Case 1 is very interesting. During the postoperative measurement of cardiac output with the patient in the head-up position, he was practically in syncope; the systolic pressure varied between 86 and 64 mm.; the diastolic auscultatory sounds were indistinct. The pulse rate during this time increased from 128 to 140 beats per minute; pallor was marked; the skin was cold and clammy, and the respirations were unusually deep and heavy, which may have had something to do with the high metabolic rate. The cardiac output decreased from an average of 2.2 in the horizontal posture to 1.09 liters per square meter per minute while he was in the 45-degree head-up posture. The stroke volume decreased from 28.2 c.c. in the horizontal, to 8.2 c.c. per beat in the head-up, posture.

Whether cardiac output can be measured accurately during such marked degrees of orthostatic hypotension as occurred in Case 1 is debatable. The acetylene method[24] for measuring cardiac output re-

TABLE II

CARDIAC OUTPUT IN 60-DEGREE HEAD-UP POSTURE

CASE	B.M.R. (PER CENT)	BLOOD PRESSURE (MM. HG)	PULSE RATE	O_2 CONSUMPTION (C.C. PER MIN.)	DIFFERENCE IN ARTERIAL AND VENOUS O_2 (C.C. PER L.)			CARDIAC OUTPUT (L. PER SQ. M. PER MIN.)			AVERAGE STROKE VOLUME (C.C. PER BEAT PER SQ. M.)
					TEST			TEST			
					1	2	AVERAGE	1	2	AVERAGE	
Preoperative											
1	- 7	156/102 148/106	92- 92	153	101.5	88.8	95.1	1.51	1.72	1.61	17.5
2*	+27	160/134 180/120	96-100	293	58.8		58.8	1.83		1.83	18.7
3	+ 5	176/116 168/110	82- 92	252	79.7	68.6	74.1	1.70	1.97	1.83	21.3
4	+ 2	154/130 146/116	134-126	193	88.9	85.0	86.8	1.44	1.50	1.47	11.9
11	+18	150/104 160/106	84- 96	214	82.3	74.0	78.1	1.78	1.99	1.89	21.0
Mean	+ 9	159/117 160/112	98-101	221	82.2	79.1	78.6	1.65	1.80	1.73	18.1
Postoperative											
1†	+27	86/ 70 64/ ?	128-140	252	143.0	114.5	128.7	0.99	1.20	1.09	8.2
2	+24	112/ 74 120/ 94	104-108	272	67.5	59.5	63.5	2.26	2.57	2.41	22.7
3	+ 2	154/100 156/110	96-100	240	91.7	41.5	66.6	1.42	3.45	2.28	22.8
4	-10	124/106 112/102	136-124	171	37.3	43.4	40.4	3.01	2.59	2.80	20.2
11‡	+ 5	144/110 138/106	108-116	183		49.6	49.6		2.64	2.64	23.6
Mean	+9.6	144/ 92 118/103	114-117	224	84.9	61.7	69.8	1.92	2.49	2.24	19.5

*This patient was somewhat uncomfortable during the preoperative studies because of thoracic pain on the left side.

†The 45-degree head-up posture was used after operation because syncope developed in the 60-degree head-up posture.

‡Case 11 is not included in the series of ten cases mentioned at the beginning of this report. In this case studies were limited to measurements of cardiac output.

quires an accurate measurement of the basal metabolic rate. It would seem that this would be difficult to obtain in instances like this, when the patient is breathing unusually heavily in an effort to improve the venous return to the heart and thus avoid syncope.

Boothby and Rynearson[26] have pointed out the essentially linear relationship between oxygen consumption and cardiac output. Harrison and Blalock[33] found in dogs that induced anoxia increased the cardiac output from 5 to 500 per cent. This, they stated, supports the hypothesis that capillary oxygen pressure is an important factor affecting circulatory minute volume. If this is true for the human being, it constitutes an important element to be considered when studies of cardiac output are done under conditions of marked circulatory stasis, such as

undoubtedly are associated with orthostatic hypotension after sympathectomy. The markedly slowed circulation time in such cases is probably associated with a certain degree of tissue anoxia which logically might affect the cardiac output. Boothby and Rynearson obtained somewhat variable results on successive measurements of cardiac output in a case of exophthalmic goiter, and suggested that this variation may represent the instability of circulation which is known to occur in such cases. We had similar experiences in the present investigation, particularly after sympathectomy. The conflicting results which have been obtained in studies of cardiac output by competent workers, using the same method, indicate the difficulties inherent in such studies.

VOLUME OF THE LEG

The purpose of this study was to note the effect of extensive sympathectomy on the volume of the leg when the patient was in the upright posture. In general, various workers[34-37] have observed that, in healthy persons, quiet standing results in increases in the volume of the leg. Turner and her co-workers[36] observed that this swelling was greater in summer than in winter. Most of the swelling appeared during the first minute of standing. Hallock and Evans[38] compared the swelling of the legs of normal persons with that of patients who had orthostatic hypotension and orthostatic tachycardia. They felt that filtration into the tissue spaces was increased in the latter group.

The volumes of the legs of four of the present series of patients, while they were standing, were estimated before and after operation. The patient inserted the leg rapidly into a steel pail especially constructed for this purpose and containing water, the temperature of which was between 86 and 95° F.; the water was essentially at the same temperature for any given patient before and after sympathectomy. The patients stood as quietly as possible for three minutes, during which time the amount of water which overflowed through the spout at the top of the pail was collected and measured. Each patient had been supine two to three hours prior to the test.

Under the conditions of this test, all four patients after sympathectomy exhibited an apparent reduction in the volume of the leg on standing, as indicated by the volume of water which was displaced (Table III). This decrease varied from 4.6 to 13.3 per cent of the total preoperative overflow value, or volume of the leg. The average reduction in volume was 7.3 per cent.

The method employed was rather crude, but it is felt that the degree and consistency of the changes are significant. The patients did not lose more than 8 to 11¼ pounds (3.6 to 5.1 kg.) between studies, which does not seem to explain fully the changes which were noted. Judging from our present knowledge of the circulation and because of the assumption that vasodilation is increased as a result of sympathectomy,

TABLE III

EFFECT OF SYMPATHECTOMY ON VOLUME OF THE LEG: CUBIC CENTIMETER WATER DISPLACEMENT, BEFORE AND AFTER SYMPATHECTOMY, ON STANDING IN A PAIL OF WATER FOR THREE MINUTES

CASE	TIME IN RELATION TO OPERATION	FASTING (HR.)	TEMPERATURE (° F.)			OVERFLOW IN 3 MIN.			WEIGHT OF PATIENT (LB.)
			MOUTH	ROOM*	WATER	TOTAL (C.C.)	LOSS		
							TOTAL (C.C.)	PER CENT	
5	Before	4½	98.6	82-80	95.0	3480			112
	22 da. p.o.	3½	98.0	80-78	95.0	3320	-160	- 4.6	?
6	Before	7	98.6	80	86.0	3320			115
	25 da. p.o.	7	99.6	80	86.5	2880	-440	-13.3	103¾
7†	Before	4½	98.6	80	89.2	3835			125
	17 da. p.o.	16	98.0	81	89.2	3665	-170	- 4.8	117
8	Before	5	98.6	78	92.1	3520			118
	20 da. p.o.	5	99.0	81	92.1	3290	-230	- 6.5	109
Mean	Before	5¼	98.6	80	90.6	3539			118
	21 da. p.o.	7⅞	98.6	80	90.7	3289	-250	- 7.3	110

*Humidity was 40 per cent before and after operation in all cases except Cases 7 and 8, in which the humidity after operation was not known.

†Patient was able to stand in a pail of water only one minute after operation because of impending syncope. At end of this period, there was only a slow dribble of about 100 drops per minute from the spout of the pail.

it would be logical to expect that the volume of the leg would be greater after sympathectomy. Why this failed to occur cannot be explained. One possible explanation might be that prolonged rest in bed incidental to the operation may have resulted in disengorgement or relative dehydration of the tissue spaces because of the decreased exposure of the legs to the influence of gravity.

COMMENT

No one knows why, as a result of the same operative procedure, orthostatic hypotension and tachycardia develop in certain cases and relatively little in others. The answer may lie in differences in constitutional make-up. It was interesting to observe that, in general, those patients who had the greatest postoperative orthostatic hypotension and tachycardia also had the greatest decreases in blood pressure and greatest increases in the pulse rate on being moved to the head-up posture before operation. For the sake of brevity, the table illustrating these observations was omitted from this paper. The number of cases studied is much too small to permit definite conclusions. Further observations along these lines seem desirable. It may be that the reaction of the blood vessels which is due to factors inherent in the vascular wall and the reaction which is due to external neurogenic influences acting on the vascular wall are present in different proportions in different persons. It may be that those patients who have marked degrees of orthostatic hypotension are the ones whose blood vessels are affected predominantly through external neurogenic influences. In such cases, sympathectomy would, perhaps, remove a relatively greater element of vasomotor control than when the intrinsic influences in the

vascular wall exert a predominant role. The fact that patients eventually recover[3] from the marked orthostatic hypotension indicates some compensating mechanism. No one knows what this mechanism is. It has been suggested[39, 40] that the sympathectomized vessels become sensitized to sympathin or epinephrine or similar humoral substances. The possibility of a certain degree of regeneration of the resected sympathetic nerves has not been excluded.[41]

SUMMARY AND CONCLUSIONS

Ten patients were studied in the horizontal and 60-degree head-up postures before and after extensive sympathectomy for essential hypertension. The important observations were as follows:

1. The pulse rate was definitely faster in every case and in both postures after sympathectomy.

2. When patients were changed from the horizontal to the 60-degree head-up posture, the systolic blood pressure fell twice as much, and the diastolic pressure fell seven times as much, after, as before, operation.

3. The difference in blood pressure between the leg and arm was little affected by sympathectomy. There was a slight tendency toward an increase in this difference after sympathectomy, which was contrary to what was expected.

4. Significant decreases in pulse pressure in the arm and leg followed sympathectomy. These decreases were greatest when the patients were in the head-up posture, and especially great among those who had postoperative orthostatic hypotension.

5. The performance of the Flack test was much impaired after sympathectomy. The greatest impairment occurred when the patients were in the head-up posture, and among those patients who had postoperative orthostatic hypotension. The systolic blood pressure during this test fell eight times as much, and the systolic rebound pressure was only two-thirds as great after operation as before operation.

6. The circulation time from arm to foot in the head-up posture decreased after operation in cases in which reductions in blood pressure were minimal to fair; it increased after operation in cases in which reductions in blood pressure were marked.

7. The circulation time from foot to arm was unobtainable in the head-up posture on the tilt table, apparently because of stagnation of the solution used for testing in the injected limbs.

8. Only those patients who had excellent reductions in blood pressure after sympathectomy had any real decrease in response to the cold-pressor test.

9. After sympathectomy the cardiac output was apparently greater in both postures. However, the cardiac output was less in the head-up posture than in the horizontal before, as well as after, sympathectomy. This difference was greater after operation, and was greatest in cases in which much postoperative orthostatic hypotension developed.

10. The stroke volume was increased in both postures after sympathectomy, but the stroke volume was always less when the patients were in the head-up posture.

11. The basal metabolic rate was decreased in both postures after sympathectomy. An actual increase in the basal metabolic rate apparently may occur while the patient is exhibiting a marked decrease in blood pressure in response to the head-up posture.

12. The volume of the leg on standing erect appeared to be decreased after sympathectomy in all cases studied; the average decrease was 7.3 per cent of the total preoperative volume. The exact reason for this unexpected observation has not been discovered.

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THE CIRCULATION IN MAN IN CERTAIN POSTURES BEFORE AND AFTER EXTENSIVE SYMPATHECTOMY FOR ESSENTIAL HYPERTENSION

II. Effect of Certain Mechanical Agents and Paredrinol on Blood Pressure and Pulse Rate*

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IN A PREVIOUS paper[1] we reported some of the physiologic effects on the circulation of extensive splanchnic sympathectomy and postural change in cases of essential hypertension. The studies to be reported in this paper were made on the same ten patients (Cases 1 to 10). In general, the same air-conditioned room and basic procedure, including the same dates of study, were employed in both instances.

This part of the investigation was concerned with modifications of blood pressure and pulse rate by (1) a tight abdominal binder, (2) bilaterally inflated cuffs around the thighs, (3) an abdominal binder plus cuffs around the thighs, (4) exercise of the legs, and (5) the administration of paredrinol sulfate. The blood-pressure-raising effects of some of these agents were compared to similar effects of the cold-pressor test. Controlled observations preceded each of the investigations. Each study was done before and after extensive sympathectomy, and, in most instances, while the patients were in the horizontal and in the 60-degree head-up postures.

TIGHT ABDOMINAL BINDER

The primary purpose of this portion of the study was to see whether such a binder would relieve the orthostatic hypotension and tachycardia which often follow extensive splanchnic denervation. The word "orthostatic" is used in this paper to denote any upright or partially upright position in which the head is higher than the feet. In most instances, this was the 60-degree head-up posture.

Various workers[2-9] have noted the beneficial effects of abdominal compression on the low blood pressure of certain persons and of animals under certain conditions when the upright posture is assumed. While studying vasomotor adaptation in animals, Hill, as early as

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TABLE I

EFFECT OF ABDOMINAL BINDER ON BLOOD PRESSURE (MM. HG.) AND PULSE RATE IN HORIZONTAL AND 60-DEGREE HEAD-UP TILTED POSTURES, BEFORE AND AFTER SYMPATHECTOMY*

CASE	PREOPERATIVE						POSTOPERATIVE						ORTHOSTATIC GAIN OR LOSS FROM BINDER	
	HORIZONTAL CONTROL		60-DEGREE HEAD-UP POSTURE				HORIZONTAL CONTROL		60-DEGREE HEAD-UP POSTURE					
			WITHOUT BINDER		WITH BINDER				WITHOUT BINDER		WITH BINDER			
	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE
1†							116/ 76	84	62/ 58	132	106/ 74	88	+44/+16	-44
2							166/ 90	84	128/ 76	100	126/ 86	104	- 2/+10	+ 4
3	220/140	88	200/130	92	206/140	96	178/120	88	164/112	100	150/108	108	-14/- 4	+ 8
4	164/120	80	146/120	96	160/120	98	150/116	88	138/100	128	116/100	112	-22/ 0	-16
5	160/100	68	164/108	88	164/110	84	184/112	96	160/110	118	182/126	114	+22/+16	- 4
6	194/124	72	198/136	90	214/140	80	194/140	104	180/138	128	204/144	128	+24/+ 6	0
7	168/114	88	154/118	112	162/134	104	160/130	108	100/ 96	152	114/104	140	+14/+ 8	-12
8	176/106	72	160/118	88	160/112	84	130/ 88	76	54/ 50	132	72/ 64	98	+18/+14	-34
9							190/130	100	164/124	108	166/128	124	+ 2/+ 4	+16
10							164/104	94	150/102	132	170/112	120	+20/+10	-12
Mean	180/117	78	170/122	94	178/126	91	163/111	92	130/ 97	123	141/105	114	+11/+ 8	- 9

*Blood pressures and pulse rates represent in almost every instance the third of a series of readings taken at two-minute intervals. The series of control readings in the horizontal posture were taken after approximately twenty minutes of rest on the table.

†After operation, patient could not tolerate the 60-degree head-up posture without syncope; hence a 40-degree head-up posture was used.

1895, found that abdominal compression prevented the syncope and death which resulted when animals were maintained in the vertical head-up posture, especially after chloroform poisoning or after splanchnicectomy. Such compression restored the blood pressure, which otherwise fell when the animal was in the head-up position. Adson and Brown[2] and Adson, Craig, and Brown[3] have noted the beneficial effects of a tight abdominal binder in counteracting the hypotension which occurs on assumption of the upright position after extensive sympathectomy.

In the present study, a many-tailed abdominal surgical binder was employed. Under the binder and over the abdomen were placed several folded towels which extended from the level of the lower ribs to the pubic region, so that, when the binder was tightened, pressure would be exerted posteriorly and upward as well as laterally against the abdomen. From two to four consecutive determinations of blood pressure and pulse rate were made at intervals of two minutes, first with the patients in the horizontal, and then in the 60-degree head-up, posture. The binder was then released, after which one or two determinations of blood pressure and pulse rate were made while the patient was still in the head-up posture. The patient was then returned to the horizontal posture. The results were compared to the control series of blood pressure and pulse rate readings which had been made in each position a few minutes previously. In some instances, the binder was tightened after its release while patients were in the head-up posture in order to note its effect under such circumstances. Six of the ten cases were studied before sympathectomy and all of the ten cases were studied after sympathectomy.

Results.—The results of this study are shown in Table I. Before operation, at the end of about five minutes in the head-up posture, the binder resulted in an average increase of 8 mm. Hg in the systolic, and 4 mm. in the diastolic, pressure, and an average decrease of 3 beats per minute in pulse rate. After operation the effect was an average increase in the systolic pressure of 11 mm., and, in the diastolic pressure, of 8 mm., and a decrease in the pulse rate of 9 beats per minute. The most striking benefit resulted when the binder was used in cases in which considerable orthostatic hypotension and tachycardia occurred, as in Case 1 (Fig. 1). In the 40-degree* head-up posture the systolic blood pressure at the end of the control period of three minutes was 62 mm., the diastolic, 58 mm., and the pulse rate, 132 beats per minute. At this time the patient was quite pale and cold and was virtually in syncope. By contrast, even at the end of seven minutes in this position, during which time the binder was tightly in place, the systolic pressure was 106, the diastolic pressure, 74, and the pulse rate, 88. The binder thus produced a net increase of 44 mm. Hg in systolic pressure and 16 mm. in

*This posture was used because more erect postures resulted in syncope.

diastolic pressure, and a decrease of 44 beats per minute in the pulse rate. The pulse pressure rose from 4 to 32 mm. as a result of using the binder.

In Case 8 the reduction in blood pressure was only fair as a result of the operation. Before operation, when this patient was in the head-up posture, the binder had little effect on the blood pressure and pulse rate. After operation, however, the binder resulted in a net increase of 18 mm. in systolic pressure and 14 mm. in diastolic pressure, and a decrease of 34 beats per minute in pulse rate. With these changes, much less pallor, clamminess of the skin, and faintness were noted, and the patient felt much stronger.

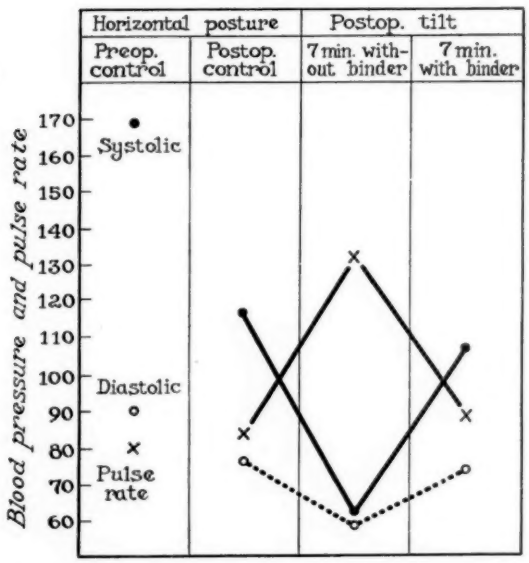

Fig. 1.—Effect of tight abdominal binder on orthostatic hypotension and tachycardia after sympathectomy in Case 1. Patient was tilted on table to 40-degree head-up posture.

In all cases after operation, release of the binder while the patient was in the head-up posture resulted in a decrease in blood pressure and increase of pulse rate, often sufficient to produce mild syncope. How much of this effect was due to reactive hyperemia and how much to other factors, such as the sudden release of mechanical support to the hypotonic intra-abdominal vascular bed, is not known. Both factors were probably present. It is interesting that patients who had the greatest degrees of postoperative orthostatic hypotension derived the most benefit from the binder. Thus, the binder appears to correct a defect that is situated, at least in part, within the abdomen, and which is an etiologic factor in the orthostatic hypotension. The most reasonable assumption is that this defect is excessive pooling of blood in the dilated, hypotonic splanchnic vascular bed. The binder probably

counteracts this tendency by indirectly supporting or compressing these reservoirs. The net effect is the establishment of a larger gradient of venous pressure between the abdomen and thorax, which results in better cardiac filling and a more favorable ratio of circulating blood volume to vascular capacity.

In Case 7 the effect of alternate tightening and release of the binder was observed while the patient was standing erect, and the results were compared with control values. As in all cases which were studied, a tightening of the binder resulted in a net increase in blood pressure, a decrease in pulse rate, and an increase in pulse pressure. Release of the binder resulted in opposite effects.

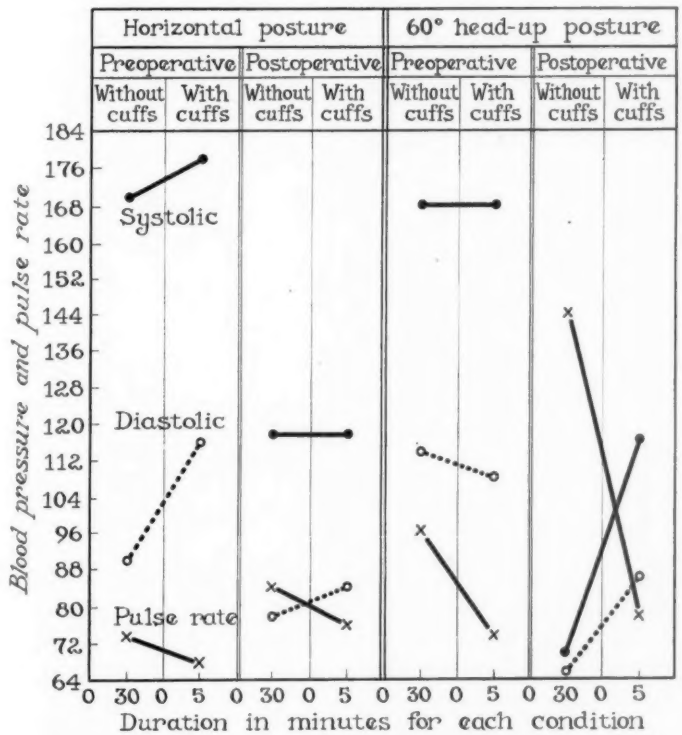

Fig. 2.—Effect on orthostatic blood pressure and pulse rate of bilateral thigh cuffs in Case 1. Patient was tilted to 40-degree head-up posture.

BILATERALLY INFLATED THIGH CUFFS

In order to study further the location of the defect responsible for orthostatic hypotension, we desired to see whether this condition could be lessened or corrected by the use of tight cuffs around the thighs, which would cut off momentarily the circulation in the legs. Stead and Ebert[10] felt that, in cases of spontaneous orthostatic hypotension, the vasoconstrictor response to a normal amount of pooling is abnormal. Other investigators have stated that perhaps there is an abnormal amount of

TABLE II

EFFECT ON ORTHOSTATIC BLOOD PRESSURE (MM. HG) AND PULSE RATE OF BILATERAL THIGH CUFFS INFLATED ABOVE SYSTOLIC PRESSURE IN THE THIGH

CASE	PREOPERATIVE								POSTOPERATIVE							
	HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE				HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE			
	WITHOUT CUFFS		WITH CUFFS		WITHOUT CUFFS		WITH CUFFS		WITHOUT CUFFS		WITH CUFFS		WITHOUT CUFFS		WITH CUFFS	
	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE
1*	170/ 90	74	178/116	68	168/114	96	168/108	74	118/ 78	84	118/ 84	76	70/ 66	144	116/ 86	78
2	200/134	84	206/150	88	190/132	96	206/130	96	164/ 88	80	160/ 84	76	140/ 76	106	146/ 82	84
3	226/140	94	218/140	96	206/136	92	218/132	100	190/134	88	204/130	86	168/110	100	206/130	94
4	166/120	80	174/136	84	156/118	92	166/134	100	150/114	84	170/130	96	136/116	128	130†/ 114†	128†
5	156/ 98	68	176/110	84	158/112	92	174/114	90	180/112	96	190/122	88	160/118	118	198/134	116
6	194/124	84	214/134	80	198/136	92	220/142	88								
7													96/ 86	140	136/122	124
8	160/108	76	190/120	76	170/112	84	176/122	84					66/ 60	112	88/ 80	84
9					138/104	80	158/110	88	190/130	100	196/126	120	166/128	108	174/140	116
Mean	182/116	80	194/129	82	173/120	90	186/124	90	165/109	89	173/113	90	125/ 95	119	149/111	103

*40-degree head-up posture was used in this case.

†Cuffs in this case were not inflated above the systolic pressure in the thigh, so that these figures in the head-up posture are not included in the final averages.

pooling of blood when such patients are placed in the head-up posture. It may be that this type of hypotension is not comparable to that which occurs after sympathectomy, for in the former the pulse usually does not accelerate to any significant degree.

Cuffs for taking blood pressure in the thighs were placed about both thighs just above the knees and inflated, while the patient was in the horizontal posture, to a point well above systolic pressure in the thigh. The patient was then moved on the tilt table to the 60-degree head-up posture, and, at the end of one minute and three minutes, the blood pressure in the arm and pulse rate were determined. One thigh cuff was then deflated, after which blood pressure and pulse rate were again determined. Then the second cuff was deflated and similar determinations were made; the patient then was returned to the horizontal posture.

Results.—Comparison with control values after sympathectomy indicates that using the cuffs resulted in an average increase in orthostatic systolic blood pressure of 24 mm., and, in the diastolic pressure, of 16 mm., with a decrease of 16 beats per minute in the pulse rate (Table II). It would appear that, in cases in which the greatest degrees of orthostatic hypotension and tachycardia occurred after operation, the blood pressure increased the most when the cuffs were employed. Thus, in Case 1 (Fig. 2), the cuffs, when the patient was in the 60-degree head-up posture, produced an increase of 46 mm. Hg in the systolic, and an increase of 20 mm. in the diastolic, pressure over the control value. The pulse rate was decreased a total of 66 beats by using the cuff. In contrast, in this case, the cuffs, when used before operation, did not produce an increase in the orthostatic systolic pressure, produced an actual decrease in the orthostatic diastolic pressure, and decreased the orthostatic pulse rate only a third as much as after operation. In all cases, release of one cuff, followed by release of the second cuff, resulted in successive decreases in blood pressure; the decline was greater after release of both cuffs than it was after release of either cuff. Obviously, effects produced by cuffs are only of academic interest, for it is not practical to use them therapeutically.

ABDOMINAL BINDER, PLUS THIGH CUFFS

Since both the abdominal binder and thigh cuffs increased blood pressure and decreased pulse rate, it seemed desirable to ascertain what effect a combination of these agents would have on blood pressure and pulse rate. They were accordingly applied and used, as previously described, on six of the ten patients, while they were in the horizontal and in the 60-degree head-up postures, before and after extensive sympathectomy.

Results.—As indicated in Table III, the combined use of these procedures on patients in the head-up posture after operation produced an average rise in systolic pressure which was twice as great as before

TABLE III

EFFECT ON ORTHOSTATIC BLOOD PRESSURE (MM. HG) AND PULSE RATE OF BILATERALLY INFLATED THIGH CUFFS PLUS ABDOMINAL BINDER

CASE	PREOPERATIVE								POSTOPERATIVE							
	HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE				HORIZONTAL POSTURE				60-DEGREE HEAD-UP POSTURE			
	WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER		WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER		WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER		WITHOUT CUFFS OR BINDER		WITH CUFFS AND BINDER	
	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE	B.P.	PULSE
1*	170/ 90	74	180/126	76	168/114	96	178/120	80	118/ 80	80	126/ 80	52	70/ 66	144	130/ 92	72
2									164/ 86	80	180/ 96	80	128/ 76	100	160/ 68	88
3					200/138	88	220/134	92	190/134	88	190/128	90	166/110	100	200/130	92
4	166/120	82	194/146	100	146/120	96	180/138	98	150/114	84	166/128	84	138/116	128	144/118	104
6	194/124	84	210/130	72	198/136	92	216/142	84	Unable to do; left thigh too sore and painful							
7									172/130	112	194/132	96	96†/ 86	164	158/134	136
8									120/ 90	70	150/100	76	54/ 50	132	120/ 94	98
Mean	177/111	80	195/134	83	178/127	93	198/133	88	152/106	86	168/111	80	109/ 84	128	152/106	98

*40-degree head-up posture used.
†Tones faint, grade 3+.

operation. The average increase in the diastolic pressure was more than three and a half times as great, and the average decrease in pulse rate was six times as much after operation as before operation. Specifically, the cuffs and binder produced an average increase of 20 mm. in the systolic blood pressure before operation and 43 mm. after operation, an increase of 7 mm. in the diastolic pressure before, and of 25 mm. Hg after, operation, and a decrease in the pulse rate of 5 beats before, and 30 beats per minute after, sympathectomy. In general, the greatest increase in blood pressure and slowing of the pulse rate after operation occurred in cases of the most severe orthostatic hypotension and orthostatic tachycardia.

COMPARISON OF EFFECTS ON ORTHOSTATIC BLOOD PRESSURE AND ORTHOSTATIC PULSE RATE OF (1) ABDOMINAL BINDER, (2) BILATERAL THIGH CUFFS, (3) ABDOMINAL BINDER PLUS THIGH CUFFS, AND (4) COLD-PRESSOR TEST

The technique for the first three procedures has already been described. The cold-pressor test was done according to the technique of one of us (Hines[11]), as outlined in a previous report. As indicated in Fig. 3, when the patients were in the head-up posture before operation, the binder, thigh cuffs, binder plus thigh cuffs, and cold-pressor test produced respective average increases in systolic pressure of 7, 13, 20, and 23 mm. Hg. After operation, the blood-pressure-elevating effects of the first three agents were about twice as great, whereas the response to the cold-pressor test was unchanged, or, in cases of postoperative orthostatic hypotension and tachycardia, was even decreased. All agents except the cold water caused a postoperative rise in diastolic pressure which was two to three times greater than the effect produced preoperatively. After operation, in the head-up posture, the binder did not affect the pulse rate, whereas the cuffs decreased it an average of sixteen beats per minute, and the binder plus cuffs decreased it thirty beats per minute. The pulse rate was not counted during the cold-pressor test in any case. Patients who had the greatest orthostatic hypotension after sympathectomy derived the greatest benefit from the use of these agents. Thus, in Case 1, binder and cuffs caused a rise in systolic pressure of 10 mm. before operation and 60 mm. Hg afterward, a rise in diastolic pressure of 6 mm. before, and 26 mm. after, operation, and a decrease in pulse rate of 16 beats per minute before operation and 72 beats afterward. The cold water caused a rise of 12 mm. in systolic pressure before operation and only 8 mm. after operation.

Comment.—If discomfort were important as a cause of the elevation in blood pressure after the use of the agents named, the cold water should elevate the blood pressure, for its pressor effect is presumed to be the result of the discomfort which it induces. If discomfort were an important factor in the effects of these agents on pulse rate and

blood pressure, such marked differences would not be expected between patients who had severe orthostatic hypotension and those who did not have this phenomenon after sympathectomy.

We might suggest as a possible explanation for the good effects of the binder and cuffs on orthostatic hypotension and orthostatic tachycardia that sympathectomy apparently decreases vasomotor tonus in a large portion of the vascular bed below the level of the diaphragm.

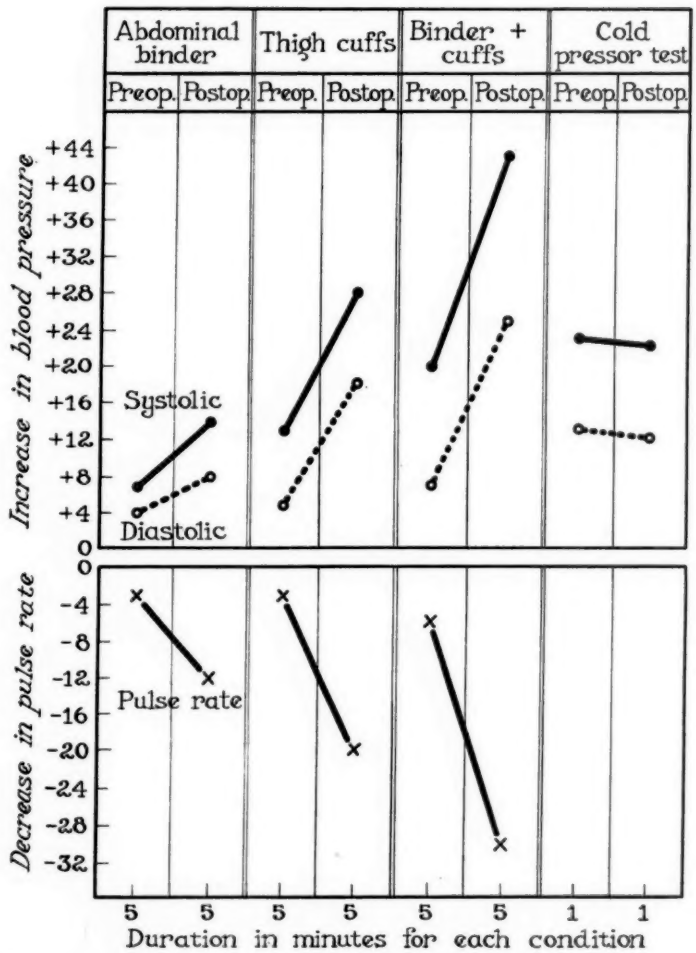

Fig. 3.—Comparative blood-pressure-raising and pulse-slowing effect of abdominal binder, bilateral thigh cuffs, abdominal binder plus thigh cuffs, and cold-pressor test before and after extensive sympathectomy. Average for all patients in 60-degree head-up posture. Values given denote deviations from control values represented by zero lines.

The vessels, as a result, become more readily distensible under the influence of the hydrostatic pressure which is brought into play by the head-up posture. The tonus which is inherent in the wall of the vessels cannot fully compensate for this force, so that, as a result,

the vessels in the regions affected by sympathectomy become more capacious, creating thereby an unfavorable disproportion between vascular capacity and circulating blood volume. The result of this would probably be an impairment in venous return and in cardiac filling, and a decrease in blood pressure and an increase in pulse rate when the patient is in the head-up posture. The increased pulse rate may be related to the decrease in blood pressure, resulting in inhibition of pressoreceptive stimuli which originate in the thoracic aorta and carotid sinuses. The marked hypotension and evidence of defective venous return to the heart seem to exclude the Bainbridge reflex as a mediator of the rapid pulse which occurs in cases of postoperative orthostatic hypotension and orthostatic tachycardia.[1] The slowing of the pulse rate, along with an increase in blood pressure when venous return is presumably improved by the use of a tight abdominal binder, supports this view. The abdominal binder probably tends partially to correct the defect responsible for orthostatic hypotension and orthostatic tachycardia by reducing the size of the splanchnic vascular resevoirs through external support to the hypotonic vessels. By this means and by the increased intra-abdominal pressure which the binder produces, the venous pressure gradient between the abdomen and thorax is presumably increased.

The cuffs, by eliminating the vascular segment below the knee, decrease the size of the vascular reservoirs and reduce the hydrostatic column against which the circulation must work while the patient is in the head-up posture. The sum total of these effects seems to be the establishment of a more favorable balance between vascular capacity and circulating blood volume, with resultant improvement in cardiac filling, cardiac output, and blood pressure. Some support for this hypothesis is afforded by the studies of Bjure and Laurell,[12] who found that, when patients with marked orthostatic tachycardia stood in water up to the level of the heart, the pulse rate did not increase. Stead and Ebert[10] made similar studies, and found that the blood pressure of patients who had orthostatic hypotension and orthostatic tachycardia was the same when they stood in water at axillary level as it was when they were in the horizontal posture. Standing in water at lower levels resulted in corresponding decreases in blood pressure. It is felt that the binder used in the present studies acted in a somewhat similar manner.

EXERCISE OF THE LEGS

It seems likely that decreased venous return to the heart is associated with the marked decreases in blood pressure and increases in pulse rate which occur when certain patients are in the upright posture after extensive sympathectomy. We wondered if active exercise of the legs, in cases in which possibly excessive pooling occurred, would counteract orthostatic hypotension by increasing venous return to the

heart. The importance of the venopressor mechanism in the circulation has been studied by Henderson and his associates.[13, 14] The role of muscle tonus in aiding venous return is well known. Freeman and Rosenblueth[15] and Pinkston and his co-workers,[16] however, noted a tendency to a decrease in blood pressure during muscular activity in dogs after total sympathectomy.

In the present study the patients stood still on the floor for three minutes. Control blood pressures and pulse rates were obtained after one and after three minutes in this position. They then rose up and down on the toes at a uniform rate of about thirty times a minute for two minutes. Blood pressures and pulse rates were obtained at the end of one and of two minutes of exercise. Within one and a half minutes after cessation of exercise, blood pressure and pulse rate were taken again. The results were compared to control values.

The effect of exercise was difficult to evaluate because it was not possible accurately to standardize the actual amount of work which was done. In two instances, exercise could not be done because the patients were on the verge of syncope at the end of the control period and had to sit down to avert syncope. Exercise apparently produced a greater increase in blood pressure before than after operation. The pulse rate during exercise increased 15 beats per minute before operation and 12 beats per minute after operation. This difference does not seem significant. In three of six cases studied, the blood pressure continued to decrease during exercise. Only in one case did the pulse rate decrease and the blood pressure increase during exercise after operation. In most cases, apparently, the good effects, if any, on the blood pressure of exercising the legs were not enough to oppose the hydrostatic pressure within vessels with decreased contractility resulting from sympathetic denervation.

PAREDRINOL SULFATE

Stead and Kunkel[17] showed that α-N-dimethyl-*p*-hydroxyphenethylamine sulfate (paredrinol sulfate) increases venous tone and venous pressure, slows the heart rate, and produces hypertension. We desired to see whether it would be helpful in counteracting excessive orthostatic decreases in blood pressure after sympathectomy, inasmuch as Stead and Kunkel found it beneficial in certain types of circulatory collapse. Accordingly, this drug was given in doses of 10 to 20 mg. subcutaneously in Cases 7 and 8 after a series of blood pressures and pulse rates were taken while the patients were in the horizontal and then in the erect posture. The drug was given about two weeks after the second stage of sympathectomy, after the patients had been walking around in the hospital for four or five days.

In Case 7 the orthostatic blood pressure was 54 mm. higher after using the drug, and the orthostatic pulse rate was 24 beats slower than the control rate. Whereas the patient was near syncope after stand-

ing for one minute before taking the drug, she had no such difficulty after fifteen minutes of standing after receiving 10 mg. of paredrinol sulfate. There was subjective, as well as objective, benefit from the use of the drug. She did not feel faint, and was comfortable except for mild cardiac palpitation caused by the paredrinol. The results in Case 7 are shown in Fig. 4. As will be seen, a decrease occurred in orthostatic blood pressure and an increase in orthostatic pulse rate,

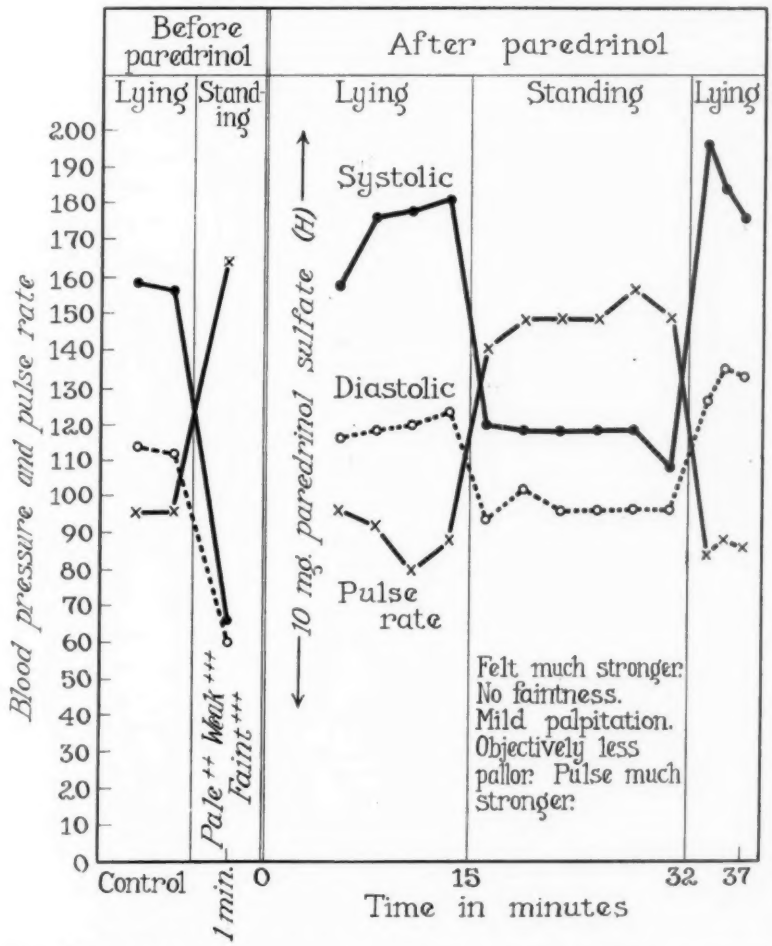

Fig. 4.—Effect of 10 mg. of paredrinol sulfate, given subcutaneously, on orthostatic blood pressure and pulse rate after sympathectomy in Case 7.

even after paredrinol had been used; the extent of these, however, was less. The level of blood pressure was raised in both postures, which seems to be the main effect of the drug. The net effect of the drug apparently was to increase the orthostatic systolic pressure 28 mm. and the diastolic pressure 20 mm., and to slow the orthostatic pulse rate 16 beats, when compared to the control values. In Case 8, the

injection of 20 mg. of paredrinol sulfate rendered the orthostatic systolic pressure 30 mm. higher and the orthostatic pulse rate 14 beats slower than the control values. It seems that paredrinol might be beneficial in counteracting excessive decreases in blood pressure when certain patients stand soon after sympathectomy, at a time when vascular adjustments are still imperfect. Stead and Kunkel found, however, that this drug tends to become less effective with repeated use.

SUMMARY AND CONCLUSIONS

Ten cases of essential hypertension were studied before and after extensive splanchnic sympathectomy. The following observations were made:

The use of a tight abdominal binder was of considerable benefit in counteracting excessive degrees of postoperative orthostatic hypotension and tachycardia. To be effective, the binder must be properly applied. The fact that the binder had little effect preoperatively or postoperatively in those cases in which orthostatic hypotension and orthostatic tachycardia were not great, but did increase the blood pressure and slow the pulse rate after operation in cases in which these phenomena occurred, suggests that the defect responsible for this condition lies, at least in part, within the abdomen.

Cuffs tightly applied above both knees in order to cut off the circulation to the legs tended to elevate the blood pressure and slow the pulse rate. This effect was greater after, than before, sympathectomy, and was greatest after operation among patients who had the greatest degrees of orthostatic hypotension and tachycardia.

The combined use of an abdominal binder and thigh cuffs had a greater blood-pressure-raising and pulse-slowing effect than either procedure alone. The effect of the tight abdominal binder, thigh cuffs, or both, in counteracting orthostatic hypotension and tachycardia was due chiefly to factors other than the discomfort which was induced by these agents.

Exercise of the legs did not produce a conclusive effect on orthostatic blood pressure and orthostatic pulse rate.

Paredrinol sulfate definitely raised the level of the postoperative blood pressure in the horizontal and erect postures, and alleviated most of the symptoms which otherwise resulted when patients were in the erect posture. It reduced somewhat the amount of orthostatic decrease in blood pressure. It may be helpful, therefore, in counteracting excessive degrees of orthostatic hypotension when patients begin to walk soon after sympathectomy.

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COMPARISON OF TOTAL VIBRATIONS OBTAINED FROM A NORMAL, RAPIDLY DYING, HUMAN HEART WITH THOSE OBTAINED IN CHRONIC MYOCARDIAL DISEASE

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WITH THE TECHNICAL ASSISTANCE OF R. E. STURM

CLINICIANS have long recognized that heart sounds may vary in quality.[1, 2] These alterations have often been defined as sounds of poor, fair, or good quality. The significance of the changes has never been well understood.

It was noted, when we were studying revived human hearts several years ago, that the heart sounds varied when the bell of a stethoscope was directly on the heart.[3] In the early period of revival the sounds were relatively long and low in pitch, and, as the ability of the heart to contract improved, they became short and higher in pitch. These observations that the sounds varied as the function of the heart improved led us to consider the advisability of recording them as a clinical method of estimating cardiac function. After study of the literature[4-6] and direct stethoscopic observations, a correlation of cardiac sounds and function seemed justifiable.

Many attempts had been made to correlate heart function with heart sounds,[7, 8] and different results were noted in the literature.[9, 10] The logical reason for such a disordered state of thought seemed to be that too much attention had been paid to the auscultatory group of vibrations and not enough to the total group. It therefore seemed advisable to record all the vibrations produced by the heart, whether audible or inaudible, rather than focus our attention on the audible group alone. It was felt that finer changes in the fundamental heart tones might be detected in such detailed study. Therefore, in order to explore this possibility, an instrument (previously described[11]) was designed with a special dynamic microphone which actuates a cathode-ray tube, the movements of which are photographed on moving paper. With such an arrangement there are no lags or overshoots, and a true reproduction of all vibrations from 1 to 500 cycles per second is obtained.

In addition to the total cardiac vibrations, the instrument records the onset of ventricular systole. Lead wires attached to the arms or arm and leg of the subject actuate the cathode-ray tube by the electrocardiographic R-wave voltage. This produces a straight vertical line in

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the vibrocardiogram at the onset of ventricular systole. The R-wave marker makes it easy to identify the cycle of the heartbeat by keeping the systolic phase oriented.[12]

A number of observations have been made with the instrument. Those by Smith, Kountz, and Edwards[13, 14] have shown that variations in vibration complexes do occur when the microphone is in direct contact with the dog's heart and the physical state of the latter is modified. The results of such controlled studies cannot be applied clinically for the reason that the chest cavity must modify the vibrations to some extent. It is necessary to establish uniformity of technique when the human heart is studied in the chest.

METHOD OF STUDY

The technique for taking records consisted of placing the subject on his back with the chest exposed, and the microphone on the thorax at any desired point. Arbitrarily we chose for this study patients whose chests were considered to be normal in contour. We used the four usual auscultation areas for obtaining total cardiac vibration curves.

In comparing the tracings of total cardiac vibrations from a large number of normal subjects and patients with outspoken or questionable heart disease, it was found that definite changes in the curves occurred when the myocardium was weakened or dilated. Briefly, these changes were characterized by a prolongation of the first vibration complex which occurred at the onset of systole and embodied the first heart sound and the appearance of large, slow, inaudible waves throughout the tracings. A preliminary study of these tracings has already been presented.[12]

In order to study these phenomena in greater detail, it was decided to approach the problem from a more basic angle. Since the heart, whether normal or diseased, attempts to adjust its output to any change in circulatory demand, a change in the force of the apex beat may often be appreciated. Tracings of total cardiac vibrations may likewise be considerably altered after activity or rest. These considerations emphasized the need of establishing a base line from which all records might be compared by first obtaining vibrocardiograms with the patient under basal conditions. The following procedure was then adopted:

A group of normal persons (100) and another group of patients with definite myocardial disease, hypertensive and coronary disease (35) were selected. A third group of 30 patients who were suspected of having early myocardial disease, or who had debilitating disease which might affect the myocardium, was also chosen. Each patient was asked to appear at the laboratory before breakfast and to lie down for an hour before the basal vibrocardiogram was recorded. After the record was obtained, the subject was given moderate exercises, and another record was taken. In all cases the tracings were obtained from the aortic, tricuspid, mitral, and pulmonic areas, and are shown in that order in the curves. The position of the pickup unit of the vibrocardiograph was

carefully marked on the patient's chest when the basal curves were obtained; the unit was placed at exactly that point when the record was made after exercise.

THE DYING HEART

In a further analysis of the influence on the curves of the physical and functional state of the heart, it seemed to us important to follow a normal human organ through its agonal period. We were able to make such an observation on a convict who died in the lethal gas chamber at the Missouri State Penitentiary. In this instance the subject was sitting when the control and agonal records were taken. Because of the straps which held the patient in the chair, the pickup was placed over the mitral area only. In addition to the vibrocardiogram, the second lead of the electrocardiogram was taken. In the observation on the convict's heart we could trace the development of myocardial weakness under conditions of anoxemia.

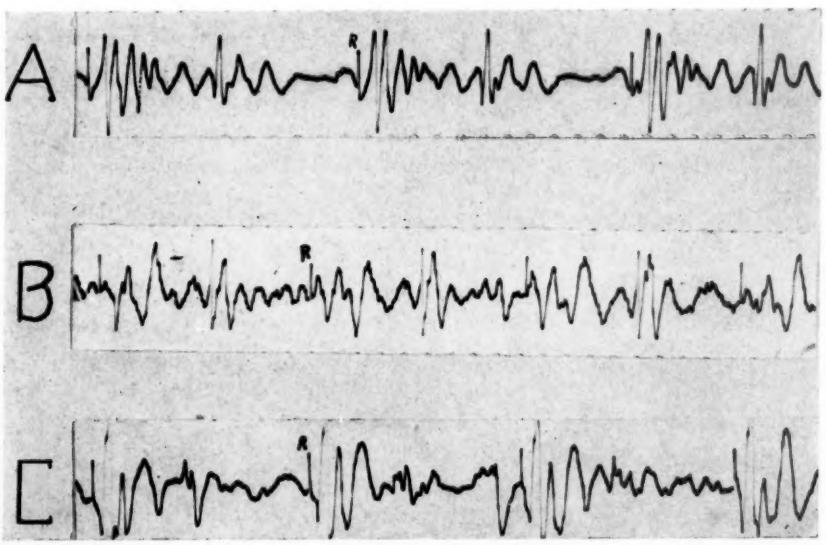

Fig. 1.—Curve *A* shows a controlled vibrocardiogram of the convict. The R-wave markers are indicated. Marked sinus arrythmia was present. The heart rate was about 95 beats per minute.

Curve *B* was taken 20 seconds after exposure to cyanide. There was an increase in heart rate to about 110 beats per minute, and slight spreading of the second component of the first vibration complex occurred.

Curve *C*, taken 30 seconds after exposure to cyanide, shows slight slowing of the heart (rate, 87). There is definite spreading of both the first and second complexes, with the loss of some of the finer vibration waves. There is, in addition, a quickening of the heart beat, and the second sound approaches closer to the first. Low frequency vibration waves are noted.

RESULTS

Fig. 1, Curve *A*, shows the control record which was taken over the mitral area on a person who was dying under conditions of anoxemia. The first sound, as in all normal records, may be divided into two

phases. The first consists of the two major vibration waves which immediately follow the electrocardiographic R wave and fall in the early part of the first sound. They are relatively high and steep, and represent the first audible portion of this heart sound. The second phase consists of waves of less frequency and amplitude. A steplike decline is thus fairly characteristic of the first sound over the mitral area.

Curve *B*, obtained 15 seconds after exposure of the convict to cyanide, shows a widening of the first phase of the first vibration complex. A slight change in the position of the man's head occurred at this point. The body position was not changed. Additional waves developed in midsystole, and some increase in heart rate occurred.

Curve *C*, taken 45 seconds after exposure to hydrocyanide acid gas, shows a further increase in the height of the first vibration component of the first complex, and a relative decrease in the second sound. There is some increase in auricular vibrations.

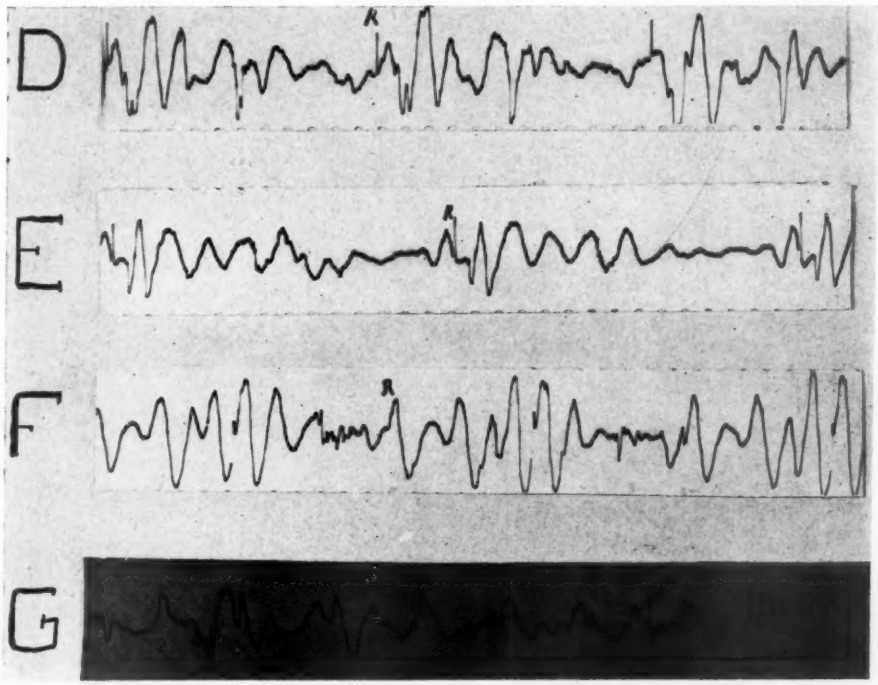

Fig. 2.—Curve *D*, taken one minute after exposure to cyanide, shows a definite spreading of all the first vibration complexes, with a negative movement of the cathode-ray as it approaches the second sound.

Curve *E*, taken 1½ minutes after exposure to cyanide, shows the development of low-frequency waves with each heart beat. The R waves may be seen preceding systole.

Curve *F*, taken 2 minutes after exposure to cyanide, is difficult to analyze, but, compared to the synchronized electrocardiogram, the R wave falls at the point labelled *R*. Throughout the contraction phase of the heart, low-frequency waves are seen. The second heart sound is masked by a gross slow movement of the cardiac vibrations. The finer vibrations are considered to be respiratory in origin.

Curve *G*, taken 2½ minutes after exposure to cyanide, shows the terminal gross movements of the heart. Relatively few vibrations are present. The fogging of the curve is due to the ammonia gas which was introduced into the chamber to neutralize the hydrocyanic acid gas.

Fig. 2, Curve *D*, shows a definite spreading of the first and second components of the first sound complex. The second sound has increased in intensity and its components have widened. This feature, however, was not consistent, and, since some respiratory spasm was present, may have been due, in part, to the changes in the air content of the chest.

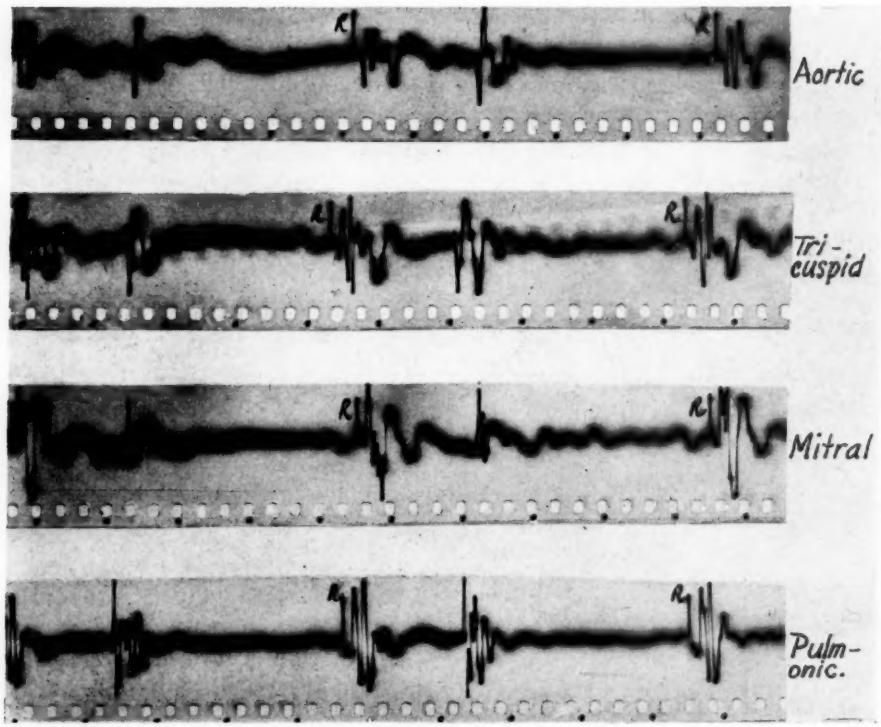

Fig. 3A.

Figs. 3A and 3B.—Vibrocardiograms of a normal subject under basal conditions and after activity. The auscultation areas from which the record was obtained are indicated. The R-wave markers are indicated on each curve.

Curve *E*, taken 2½ minutes after exposure, shows definite slowing of the heart. In the first complex there are loss of the first vibration components and an apparent widening by fusion of the first and third ones. Low frequency waves may be seen coming in at this point. The first change noted in the electrocardiogram occurred at this time, and appeared rather suddenly as a lowering and flattening of the T wave.

Curve *F*, taken 3½ minutes after exposure to cyanide and 30 seconds after the final respiratory effort, shows low frequency systolic and diastolic waves. These waves are not unlike those found in experimental animals and in patients with acute coronary artery occlusion.

Fig. 3 shows the vibrocardiogram of a normal subject under basal conditions and after activity. Definite changes of two types may be seen in the curve. First, the initial vibration complex, beginning with ven-

tricular systole, is more sharply defined after activity, and, compared with the normal curve, the vibration group as a whole tends to be of slightly lesser duration. These particular changes almost invariably occur in tracings from normal subjects. Occasionally one sees low-frequency waves in systole and diastole, often most prominent at the aortic or tricuspid areas. In the present series, this occurred in five cases.

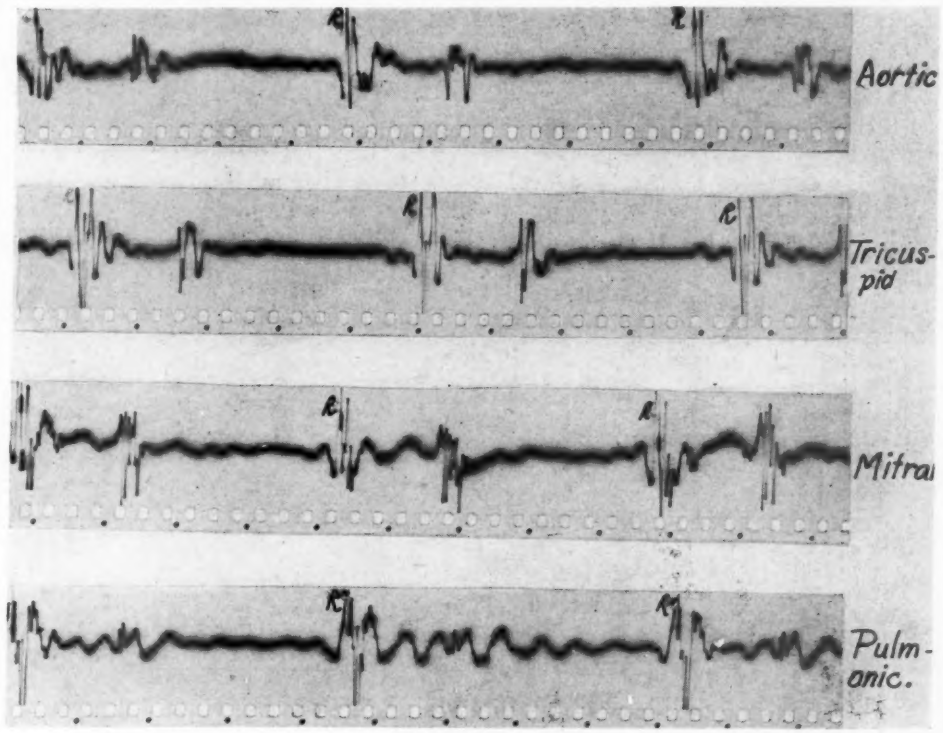

Fig. 3*B*.

However, when there are low frequency waves in the basal curves, they tend to diminish or disappear entirely in the tracings after activity. From an examination of the curves, one finds that, in persons who appear to be normal, activity results in an intensification of the first vibration complex, which becomes sharper and more steep, and is broken by quick movements of the beam. The second heart sound vibrations likewise become sharper by virtue of an increase in blood pressure.

Vibrocardiographic curves from patients with myocardial disease (hypertrophy and dilatation) showed constant modifications.

A typical curve from this group of patients is shown in Fig. 4. The curve was obtained from a 66-year-old woman who had been treated for gall bladder disease, but had suddenly suffered extreme precordial pain, a gradual fall of blood pressure, and fever. Electrocardiographic studies, made at that time, showed definite evidence of myocardial in-

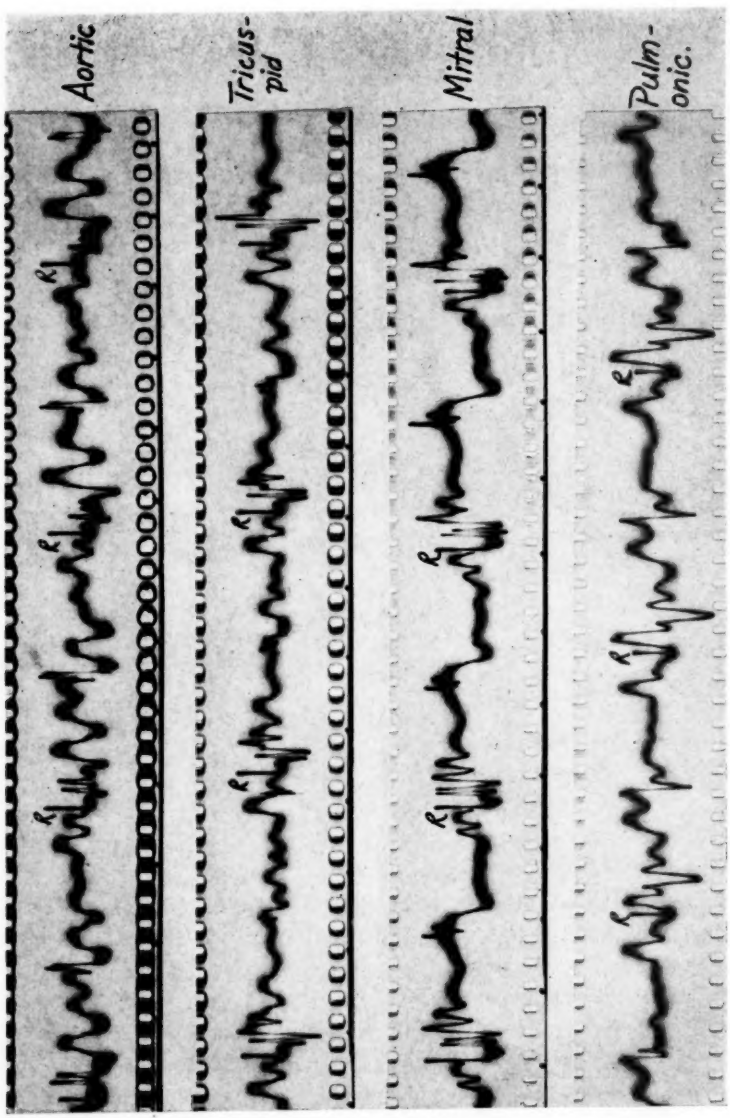

Fig. 4A.

Figs. 4A and 4B.—Fig. 4A shows the vibrocardiogram of a patient who had had myocardial infarction (taken under basal conditions). Fig. 4B is the record taken after activity. The R-wave marker and auscultation areas from which the tracings were obtained are indicated. Note the low-frequency elements in the basal curve and their accentuation after activity in all the tracings.

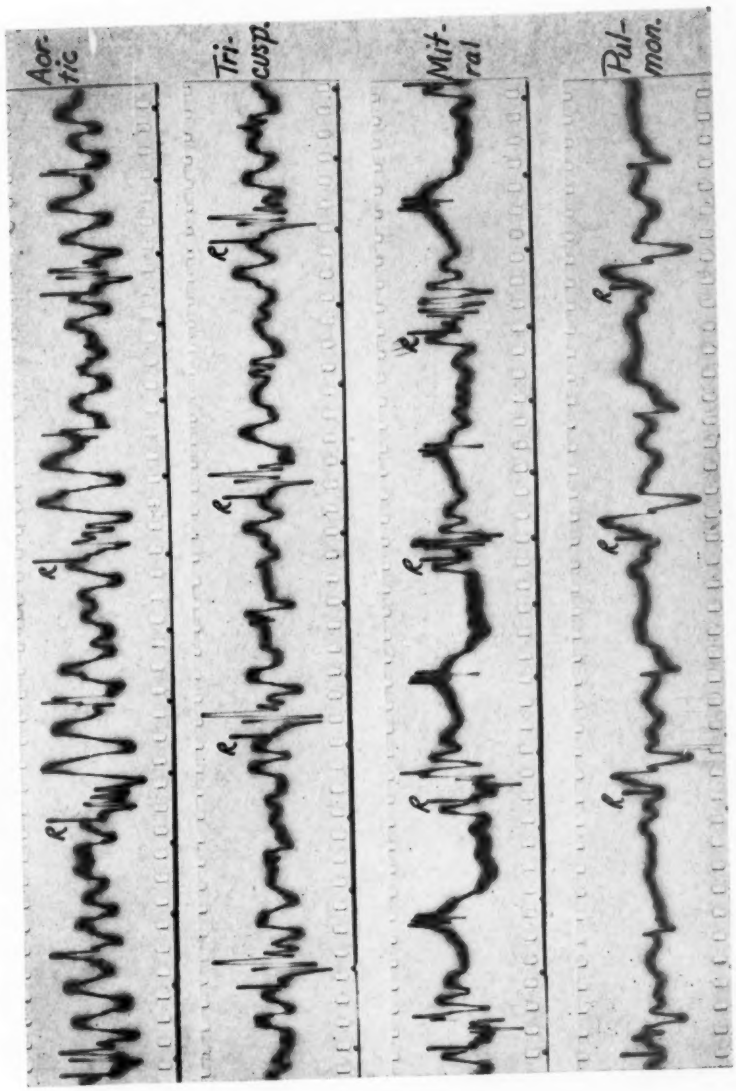

Fig. 4B.

farction. A kymogram six weeks later revealed no general cardiac enlargement, but showed reduced excursions of the heart and aneurysmal dilatation of the left ventricular wall. The vibrocardiogram which was taken under basal conditions was in marked contrast to a normal curve (Fig. 3). The most interesting feature of the tracing is the prominence of large, low-frequency waves which dominate the first and second vibration complex. As clearly shown in the illustration, the complexes appear spread, with rounded peaks. Indeed, when one listens to such a heart the first sound often seems muffled and distant and of "poor quality." When the patient had been "active" throughout the morning, the changes in the curves were usually even more accentuated. The low-frequency, inaudible waves became more prominent, and the first vibration complexes were more blunt and spread. The entire tracing appeared to consist largely of rounded waves and low amplitude ripples of various frequencies. These changes in the conformity of the curve persisted even though the pulse rate was at nearly the same level as when the patient was under basal conditions.

Patients who showed changes in the vibrocardiograms alone make up our third group. This group, consisting of 30 patients, presented symptoms which pointed to some myocardial impairment, but were not severe. Ten of the patients suffered from a mild form of angina pectoris. The others had rheumatic or syphilitic heart disease or showed evidence of early cardiac weakness associated with hypertension. Some had severe anemia or infection, without definite clinical evidence of cardiac disease. Vibrocardiographic records were obtained on all of these patients before, or immediately after, treatment had been instituted.

In some of these patients, "abnormal" changes were evident in the curves taken under basal conditions, but, in others, alterations in the curves were brought out only after the patients had been active.

Fig. 5 shows a typical instance of these changes in the vibrocardiographic curves from a subject with no clinical evidence of heart disease. This patient, a 28-year-old white woman, was under treatment for primary anemia, syphilis, and general undernutrition. At the time the record was made the erythrocyte count was 3,000,000, and the hemoglobin was 63 per cent. The kymogram showed that the heart was of normal size, with excursions of essentially normal scope. The electrocardiogram was considered indeterminate. The curve of total cardiac vibrations which was taken under basal conditions showed somewhat abnormal contour of the deflections; the first vibration complexes were tall and somewhat spread. After activity, the curves recorded from the same locations on the chest wall were definitely altered. The first vibration complexes were marked by slopes of lesser steepness, and large, inaudible waves occurred in systole and diastole. The latter simulated the changes seen in advanced myocardial disease, and were not unlike some of the waves recorded from the dying human heart. Since it is

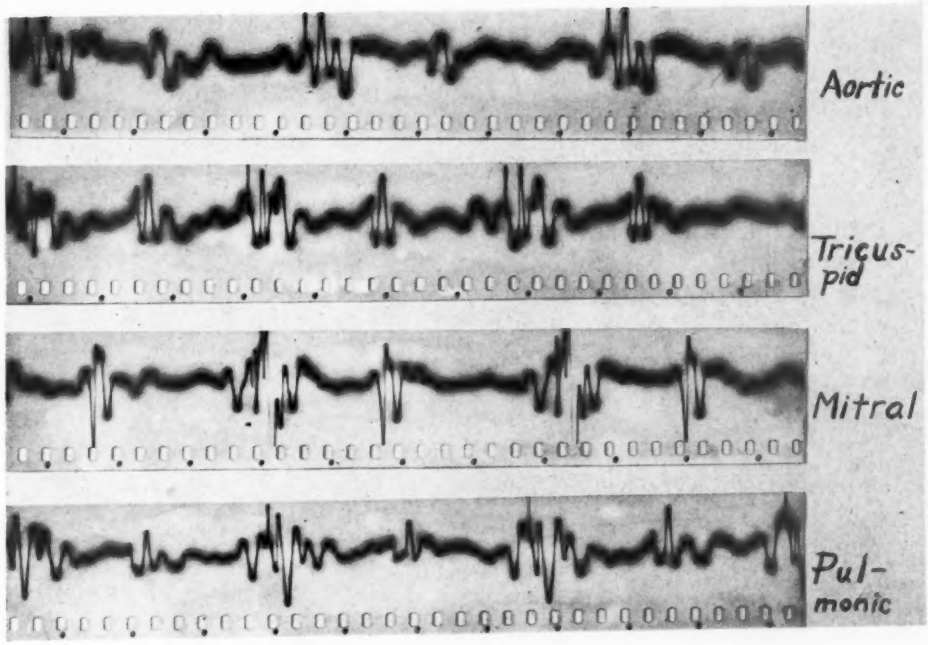

Fig. 5*A*.

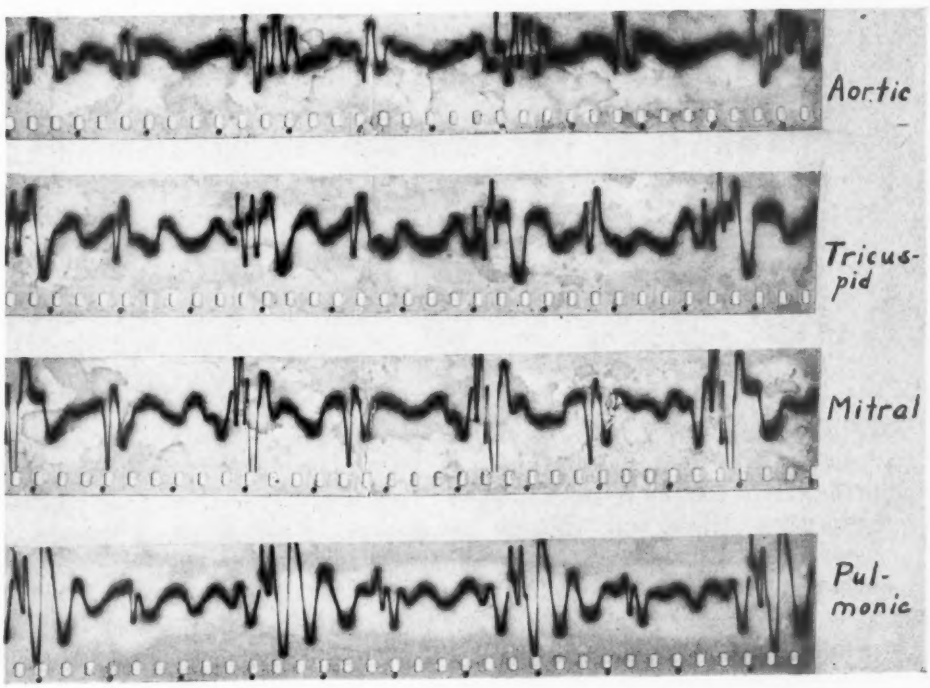

Fig. 5*B*.

Figs. 5*A* and 5*B*.—Fig. 5*A* is a vibrocardiogram of a patient who had only slight clinical evidence of heart disease. The corresponding auscultation areas and R-wave markers are indicated. After activity (Fig. 5*B*), the low-frequency waves became more prominent, and there was some spreading of the first vibration complex in the aortic and tricuspid areas.

known that the heart may suffer from one or all three of the debilitating conditions which this patient presented, it was considered probable that these alterations were due to secondary changes in the heart muscle.

DISCUSSION

One should not forget that total cardiac vibrations may be expected to differ from heart sound vibrations alone. The type of curve and the component parts are entirely different. The inherent difference between total cardiac vibration records and audible records should be borne in mind when one attempts to analyze the curves.[15]

The normal vibrocardiogram, from any auscultation area, consists of vibration components which may be roughly divided into two dominant vibration groups.

The first group of deflections immediately follows the R-wave marker, and begins with the onset of ventricular contraction. The vibrations are tall and peaked, with steep slopes which represent the audible element of the first heart sound. The second heart sound, which is caused by closure of the semilunar valves, is recorded as a group of sharply pointed deflections, sharper in profile and of somewhat lesser duration than the first vibration group. A number of small "preliminary waves" frequently occur in advance of the first vibration (just preceding the R-wave marker), and are thought to be due to auricular contraction; the preliminary waves are usually best seen in tracings from the tricuspid area. In about 5 per cent of normal tracings, very low frequency ripples, below auditory level, occur. In most curves, these low, smooth undulations seem to be in phase with each other and with the onset of systole. The phenomenon is usually more prominent in persons who are debilitated. It is in the character of these low-frequency, inaudible waves that the most striking changes occur in myocardial disease.

It is to be emphasized that, in our cases, the changes in vibration complexes and the appearance of large, slow waves in patients who were known to have myocardial disease were frequent before the institution of therapy. As our vibrocardiographic studies progressed, it became evident that patients who had suggestive or outspoken signs of myocardial disease, but showed no other laboratory abnormalities indicating cardiac abnormality, often exhibited changes in the total vibration curves. The changes went so far as to be comparable to those from patients with definite heart disease. Some patients who had no signs of heart disease, but were suffering from severe anemia or infections which affect the heart muscle, frequently showed vibrocardiographic changes.

The variation of total vibrations of the heart when the physical and functional state declines is established. The dying human heart under conditions of anoxemia produces a continuous change in the pattern of total cardiac vibration curves. These vibration complex curves have a general resemblance to those obtained from the precordial area of patients with heart disease.

The chest does modify the experimental and clinical cardiac vibration curves. The chest factor is, however, fairly constant, and, provided the shape of the chest is normal, and respiration is quiet, only minor variations are attributable to respiratory factors. An extreme variation in the relationship of the heart to the chest wall does modify cardiac vibrations, and precaution should be taken to eliminate this influence. The curve of the total cardiac vibrations from a normal chest without respiratory effort has been sufficiently constant to be considered standard, and thereby to establish a general pattern, as has been previously reported.

The fact that the cardiac vibrations are extremely sensitive to variations in the physical and functional state of the heart suggests the possibility of their use in the early recognition of heart disease. Our observations indicate that changes in vibrations occur early in heart disease, and suggest that further study and clinical correlation should be directed to establishing their value in early heart disease. Attempts must be made to bring the degree of cardiac and chest activity to a minimum. Hence the basal state is important. Changes in the curves produced by graded, increased activity of the subject throws light on a heart's ability to respond to an increased load. Such changes in the total cardiac vibration curves as spreading of the first complex, decrease in the amplitude of the first complex, and development or increase of low frequency waves during systole or diastole occur when the work of the heart is increased.

SUMMARY

The curves of total cardiac vibrations, recorded by means of a cathode-ray tube, were obtained from a dying convict's heart, from persons who were known to be normal, from patients with heart disease, and from persons who were suspected of having heart disease. The changes in the total cardiac vibrations from the dying human heart and from patients with heart disease have similar features. Spreading, especially of the first and second components of the first complex, was noted. Low-frequency systolic and diastolic waves developed under both clinical and experimental conditions, and suggested, as had been previously suspected, disordered cardiac function.

The authors wish to express their appreciation to Paul E. Kaiser, Warden of the Missouri State Penitentiary, and to the many officials who made possible part of this study.

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THE DELAYED DIASTOLIC MURMUR ASSOCIATED WITH VENTRICULAR ECTOPIC BEATS. PHONOCARDIOGRAPHIC STUDIES

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PROVIDENCE, R. I.

IT IS well known that when ventricular ectopic beats occur early in diastole, the diastolic phase of the normal beat is replaced by the ectopic beat. However, under these same conditions in mitral stenosis and aortic insufficiency, in which there is a diastolic murmur, there is a delay in the appearance of the murmur. The diastolic murmur is now found during the diastolic phase of the ventricular ectopic beat. This same delay will probably be found in diastolic murmurs associated with corresponding lesions of the tricuspid and pulmonary valves. If one is not acquainted with this delay in the appearance of the murmur after the normal beat, one may think that all the sounds heard during ventricular extrasystoles are part of the ectopic beat.

Phonocardiograms were taken to illustrate the delayed murmurs. The first illustration was taken with the electrocardiogram as a reference tracing (Fig. 1). Sound tracings were taken at the apex to show the delayed diastolic murmur in mitral stenosis. The second set of records was made at the same area, with the apex cardiogram as a reference tracing (Fig. 2). The third set was taken at the second right intercostal space to show the delayed diastolic murmur in aortic regurgitation (Fig. 3). In this set the jugular tracings were used for reference.

The upper phonocardiograms in each set were made by the stethoscopic method, and the lower by the logarithmic method described by Rappaport and Sprague.[1] The numbers *1* and *2* indicate the first and second heart sounds, and *s.m.* and *d.m.* indicate the type of murmur.

All of the records were made on the same patient. He was a 27-year-old white man who had mitral stenosis and insufficiency as well as aortic stenosis and insufficiency. The electrocardiograms showed auricular fibrillation, ventricular ectopic beats from multiple foci, coupling, and right axis deviation. He had had too much digitalis. After the digitalis was stopped, the ectopic beats disappeared. At this time he had the usual murmurs in their regular places.

It is to be noted that there was an accentuation of the mitral diastolic murmur during the rapid inflow of blood into the left ventricle in the diastolic phase of the ectopic beat.

From the Rhode Island Hospital and Providence Lying-In Hospital.
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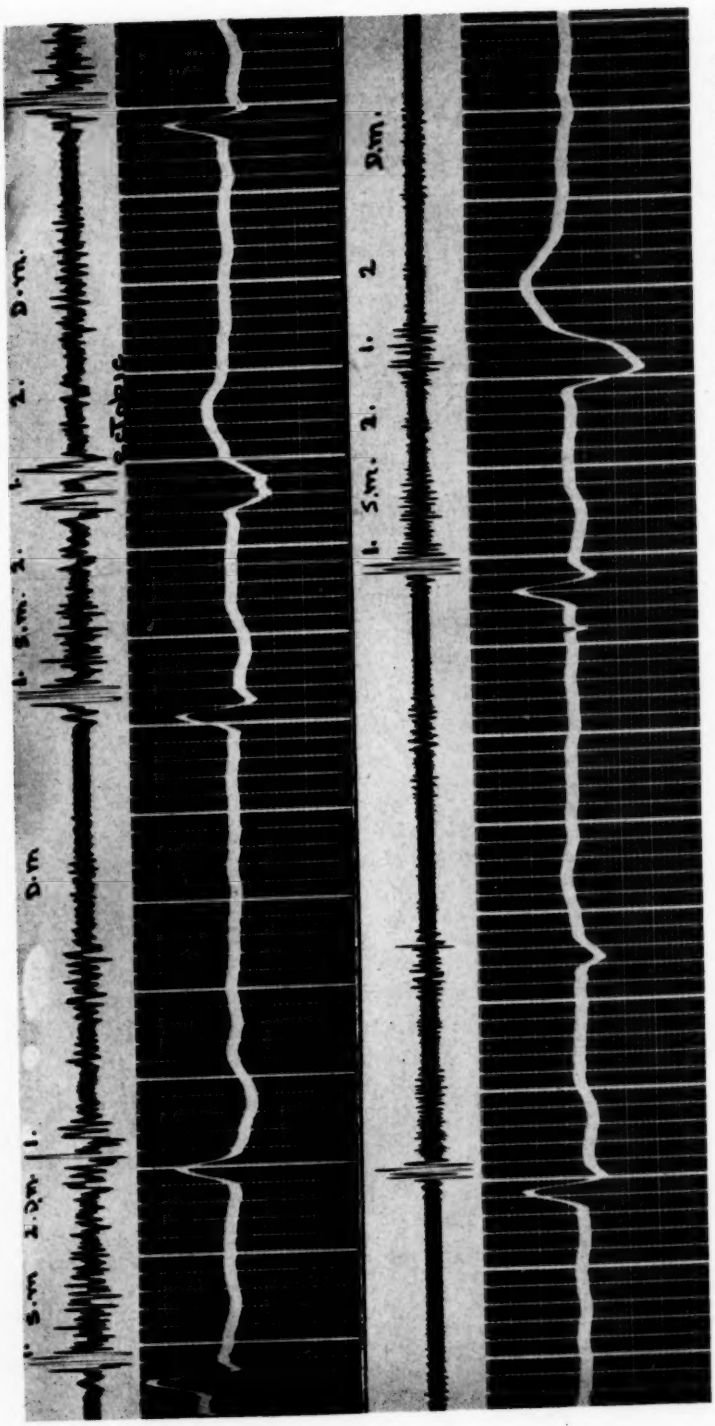

Fig. 1.—Phonocardiograms with the electrocardiogram as reference tracing. The upper record was made by the stethoscopic method and shows the low frequency sounds best. The lower record was made by the logarithmic method. The sounds recorded by this method are within human audibility and are similar to those heard when using an acoustic stethoscope. Note the diastolic murmur during diastole of the ectopic beat.

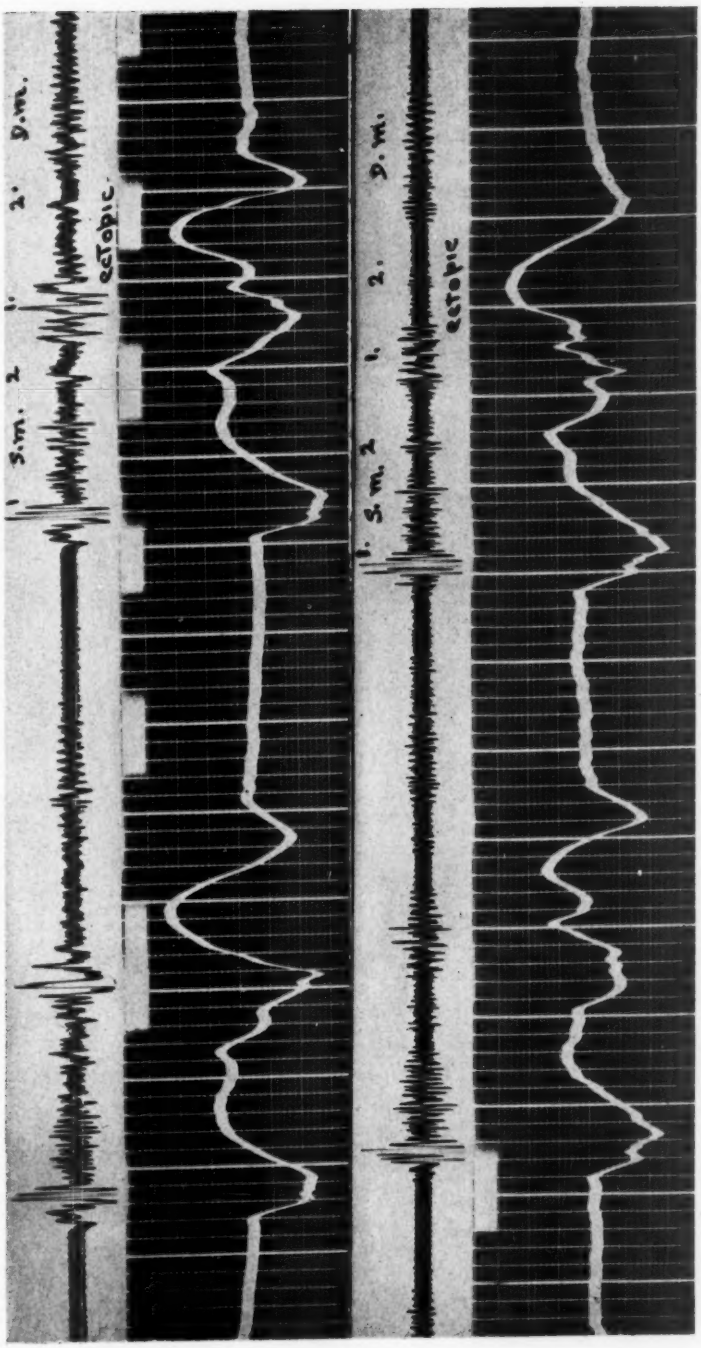

FIG. 2.—Phonocardiograms and apex cardiograms (linear tracings). The upper record was made by the stethoscopic method and the lower by the logarithmic method. The delayed mitral diastolic murmur is shown during the diastolic phase of the ectopic beat. The murmur begins at a definite interval after the second sound. It is loudest during the time of rapid inflow.

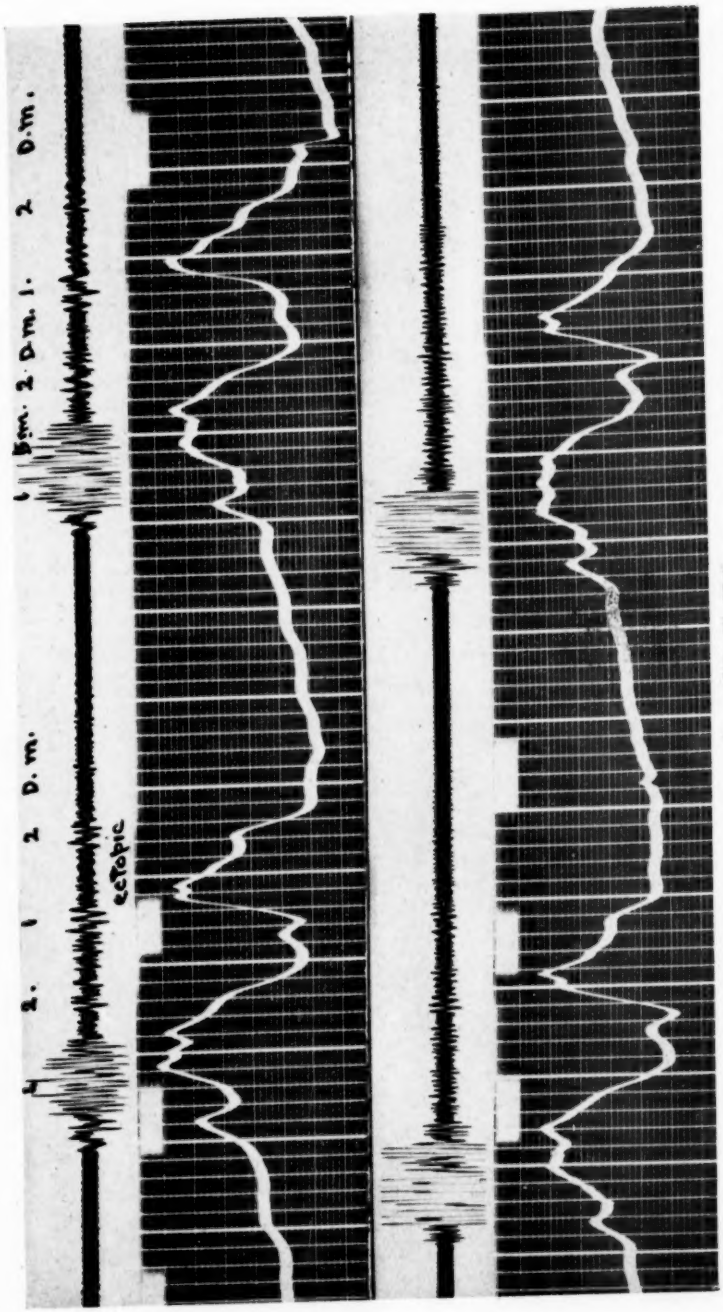

Fig. 3.—Phonocardiograms and jugular tracings. The upper record was made by the stethoscopic method. The lower record was made by the logarithmic method. The phonocardiograms are from the second right intercostal space. Note the aortic diastolic murmur in the diastolic phase of the ectopic beat. It is continuous with the second sound.

This same accentuation has been noted during the time of rapid inflow in mitral stenosis without ectopic beats. There is also an increase of loudness at the time of the auricular beats. Pericardial friction rubs show the same characteristics. Therefore, in interpreting phonocardiograms, as well as electrocardiograms, one should know the clinical findings.

Although there was aortic regurgitation in this case, the predominant murmur at the apex was that of mitral stenosis. The murmur began a short interval after the second sound, and occurred for the most part in the diastoles of the ectopic beats because of the coupling in this case.

The aortic diastolic murmur was of higher frequency, and followed directly after the second sound in the ectopic beats, just as it does with normal sinus rhythm.

The low frequency murmur was best illustrated in the tracings made by the stethoscopic method. Since the aortic diastolic murmur was of higher frequency, it was best seen in the tracings taken by the logarithmic method.

SUMMARY

By a delayed diastolic murmur is meant a murmur that cannot come at its usual time in diastole because of the occurrence of ventricular ectopic beats. Therefore, the murmur is delayed until the diastolic phase of the extrasystole.

This delayed murmur is usually not recognized because it comes so long after the normal beat, and the sounds are associated with the ectopic beat itself.

Phonocardiograms were made to illustrate this point in both mitral stenosis and aortic regurgitation.

The possibility that such delayed diastolic murmurs may also be associated with lesions of the right side of the heart is suggested.

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Clinical Report

MYOCARDITIS CAUSED BY EPIDEMIC PAROTITIS

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MAJOR JOHN NOLL, JR., MEDICAL CORPS
ARMY OF THE UNITED STATES

INTRODUCTION

EPIDEMIC parotitis has been recognized as a clinical entity since antiquity, and such complications as orchitis, meningoencephalitis, and pancreatitis have been reported by many medical observers since that time. However, it was not until 1918 that attention was first called to the possibility that myocarditis might result therefrom. In that year, Pujol,[1] a French military surgeon, described three cases in soldiers, in which, because the patients developed dyspnea or substernal pain after recovery from mumps, he suspected that the myocardium had been affected by that disease. Unfortunately, no electrocardiographic studies or other corroborative data were available at that time. In 1932, the examination of post-mortem material prompted Manca[2] to state "the mumps virus can attack the heart, and the lesion consists of an acute interstitial myocarditis, especially characterized by a fibrinous exudate which differentiates it from other forms of myocarditis, and may be considered as a peculiarity of this infection"; this definitely established the possibility of cardiac complications in mumps. Nevertheless, the electrocardiographic demonstration of such a complication during the convalescent period of mumps has, until now, been lacking. For this reason a cardiac survey of fifteen soldiers who were recovering from this illness was undertaken by the authors. In this group, one instance of acute myocarditis was discovered. This is described in detail because its importance is obvious, not only to civilian practitioners, but also to military surgeons who encounter mumps in the epidemic proportions which it frequently assumes in time of war.

CASE REPORT

A 19-year-old soldier was admitted to the Station Hospital, AAFTTC Chicago, March 23, 1943, because of a swelling under the left side of the jaw and in front of the right ear. This swelling had first been noted by the patient the day before. He had otherwise been well. His past medical history was essentially unimportant, and he never suffered from joint pains, chorea, or heart disease. Physical examination at the time

From the cardiac section of the medical service, Station Hospital, AAFTTC, Chicago, Ill.
Received for publication July 5, 1943.

TABLE I

DATE	SIGNIFICANT ELECTROCARDIOGRAPHIC DATA	REMARKS	DAY OF DISEASE
3/30/43	Heart rate, 48; flattening of T_2; inverted T_3; P-R, 0.16 sec.	Temperature normal; clinical examination of heart negative; parotid swelling almost entirely absent: no arthritic manifestations	8th
4/ 4/43	Heart rate, 68; T_2 upright; T_3 diphasic; P-R, 0.16 sec.	Temperature normal; all parotid swelling has disappeared; clinical examination of heart negative; no arthritic manifestations	13th
4/ 8/43	Heart rate, 63; T_2 upright; T_3 diphasic; P-R, 0.16 sec.	Temperature normal; teleoroentgenogram reveals normal heart; clinical examination of heart negative; no arthritic manifestations	
4/13/43	Heart rate, 68; T_2 upright; T_3 diphasic; P-R, 0.28 sec.	Temperature 100° F. all day; clinical examination of heart negative; sedimentation rate, 42 mm. in one hour; no arthritic manifestations	
4/14/43	Heart rate, 83; T_2 upright; T_3 diphasic; P-R, 0.28 sec.	Temperature normal; sedimentation rate, 34 mm. in one hour; no arthritic manifestations; clinical examination of heart negative	
4/17/43	Heart rate, 68; T_2 upright; T_3 upright; P-R, 0.32 sec.	Temperature normal; sedimentation rate, 25 mm. in one hour; clinical examination of heart negative; no arthritic manifestations	
4/23/43	Heart rate, 80; T_2 upright; T_3 upright; P-R, 0.20 sec.	Temperature normal; sedimentation rate, 20 mm. in one hour; no arthritic manifestations, clinical examination of heart negative	
5/ 4/43	Heart rate, 68; T_2 upright; T_3 diphasic; P-R, 0.16 sec.	Temperature normal; sedimentation rate, 12 mm. in one hour; no arthritic manifestations; clinical examination of heart negative	
5/18/43	Heart rate, 70; T_2 upright; T_3 diphasic; P-R, 0.18 sec.	Temperature normal; sedimentation rate, 10 mm. in one hour; no arthritic manifestations; clinical examination of heart negative	

TABLE II

EFFECT OF ATROPINE SULFATE (GR. 1/25) ADMINISTERED INTRAMUSCULARLY

INTERVAL AFTER EXHIBITION OF ATROPINE SULFATE	ELECTROCARDIOGRAPHIC DATA
Control (before injection of drug)	Normal sinus mechanism; P-R, 0.30 sec.; heart rate, 83
10 minutes after	Auriculoventricular dissociation; auricular rate, 79; ventricular rate, 88
20 minutes after	Normal sinus mechanism; P-R, 0.24 sec.; heart rate, 107
30 minutes after	Normal sinus mechanism; P-R, 0.28 sec.; heart rate, 125
40 minutes after	Normal sinus mechanism; P-R, 0.36 sec.; heart rate, 142

of his admission was essentially negative except for a slight, spongy swelling over the right parotid region and under the left side of the jaw. There were no significant abnormalities of the heart. The diagnosis of mumps was confirmed by the medical officer in charge of the

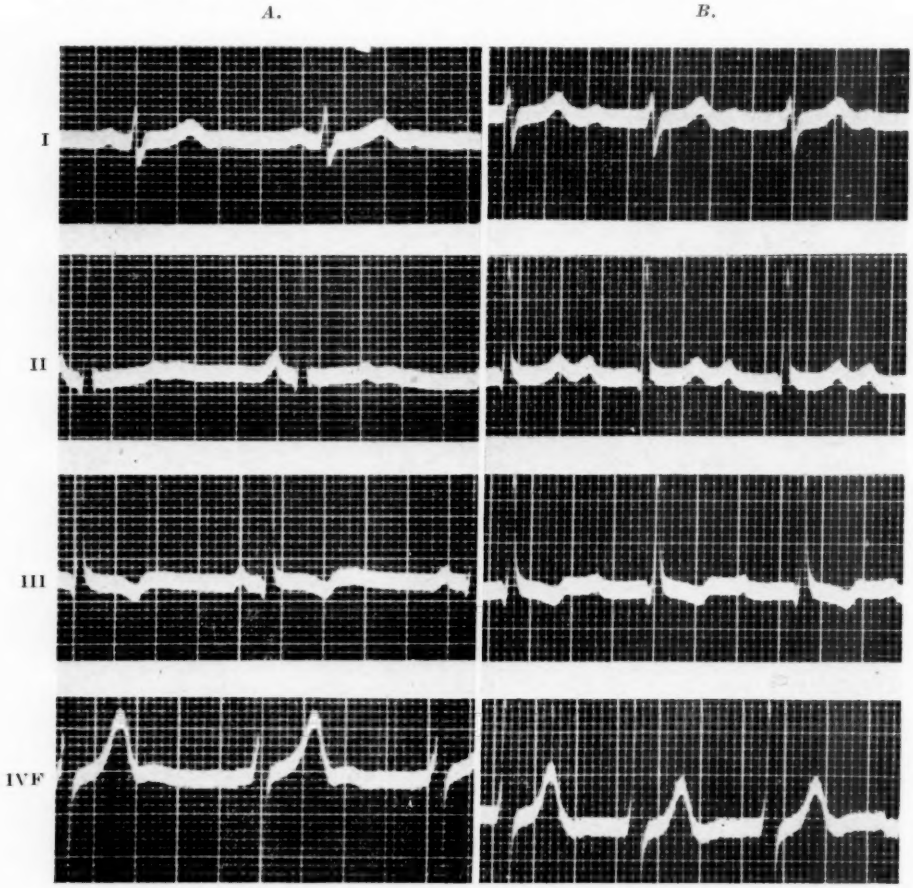

Fig. 1.

contagion ward. The patient's progress in the hospital was uneventful, as attested by the following notes:

March 24, 1943.—Swelling in the original area has increased a little. No new involvement. No complications.

March 27, 1943.—Swelling is subsiding. No new involvement. No complications.

March 29, 1943.—Swelling continues to subside. No complications.

April 2, 1943.—All swelling has disappeared. No complications.

April 4, 1943.—Uneventful convalescence.

On March 30, 1943, a routine electrocardiogram was obtained (Fig. 1, *A*). It will be noted that the only abnormalities consist of flattening of the T wave in Lead II and sinus bradycardia. In a subsequent electrocardiogram, five days later, the abnormal T pattern and bradycardia had disappeared. On April 13, 1943, the electrocardiogram showed first degree A-V heart block, with a P-R interval of 0.34 second (Fig. 1, *B*). Other records were obtained at frequent intervals, and the data from these tracings are summarized in Table I. The effect of atropine sulfate on the delayed A-V conduction was observed April 15, 1943, and the results of this experiment are recorded in Table II. The last electrocardiogram, which was obtained May 18, 1943, was entirely normal, and the patient was returned to duty May 22, 1943.

During the entire period of his hospitalization the patient never presented any symptoms suggestive of cardiac disease. No other complications of mumps occurred. He never complained of joint pains. The temperature remained normal during most of the hospital stay; it was elevated only in the early phases of the disease. The range of the body temperature and of the erythrocyte sedimentation rate, in relation to the clinical course and the electrocardiographic manifestations of active myocarditis, is recorded in Table I. The heart shadow in two teleoroentgenograms was not abnormal. The blood pressure was never elevated.

DISCUSSION

The diagnosis of acute myocarditis as a complication of mumps can hardly be questioned in this instance, even though clinical signs and symptoms of cardiac disease were lacking. The T-wave changes and the sinus bradycardia in the original tracing might be considered of equivocal significance, but the definite, although transient, prolongation of the P-R interval surely supports such a diagnosis. In addition, the temporary shortening of the A-V conduction time produced by atropine (Table II) is a type of response similar to that which occurs in cases of first-degree heart block secondary to active rheumatic carditis.[3-5] It is, therefore, reasonable to suppose that a myocarditis of the type described by Manca[2] was probably the cause of the electrocardiographic alterations in this case. So far as we are aware, this is the first reported instance in which excessive vagal tone was shown to contribute to prolongation of the P-R interval when the latter was the result of nonrheumatic myocarditis; this emphasizes the nonspecific nature of this particular electrocardiographic abnormality.

The incidence of cardiac complications in cases of mumps may be higher than is ordinarily supposed, inasmuch as significant electrocardiographic changes were found in one of fifteen soldiers with the disease. This figure may possibly be modified in future surveys of larger numbers of subjects. It is therefore planned, if possible, to investigate this phase of the problem more intensively during the next epidemic of the disease.

It is also of interest that the myocarditis under discussion occurred without any clinical signs or symptoms, and developed independently of

any of the usual complications of mumps. This implies that perhaps many instances of this complication have been overlooked in the past. It will be noted (Table I) that it was associated with an increased erythrocyte sedimentation rate. Therefore, it is recommended that this laboratory procedure be used routinely in every case of mumps during convalescence, and, if the rate is elevated, an electrocardiogram should be obtained to establish or eliminate the possibility of a complicating myocarditis.

SUMMARY AND CONCLUSIONS

1. The first known case of myocarditis complicating mumps, in which the diagnosis was established during life, is described.

2. The importance of the routine use of the electrocardiograph in the diagnosis of this complication is emphasized.

3. The similarity of the electrocardiographic changes to those which result from acute rheumatic myocarditis is demonstrated and briefly discussed.

4. The asymptomatic nature of the myocarditis and its occurrence in the absence of the usual complications of mumps are emphasized. Attention is also called to the possibility that, for this reason, many such cases are overlooked.

5. It is suggested that, in the absence of the usual complications, a persistent increase in the erythrocyte sedimentation rate in cases of mumps, after the parotid swelling has subsided, justifies the routine use of the electrocardiograph to eliminate the possibility of a complicating myocarditis.

6. In a random selection of fifteen cases of epidemic parotitis, the incidence of complicating myocarditis was found to be 6.7 per cent.

7. Wider use of the electrocardiograph in cases of mumps in various stages of the disease is recommended in order to establish definitely the incidence of cardiac complications, and hence the optimum period for complete convalescence.

8. Our experience in this case indicates that functional recovery from myocardial involvement in mumps may be complete.

REFERENCES

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2. Manca, C.: Myocarditis From Epidemic Parotitis, Arch. ital. di anat. e istol. pat. **10**: 716, 1932.
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5. Wendkos, M. H., and Noll, J.: A Survey of Rheumatic Fever in a Large Station Hospital, M. Clin. North America **28**: 124, 1944.

Abstracts and Reviews

Selected Abstracts

Hueper, W. C.: Experimental Studies in Cardiovascular Pathology. IX. Reactions in the Blood and Organs of Dogs on Intravenous Injection of a Solution of Glycogen. Arch. Path. **36**: 381, 1943.

A solution of glycogen injected intravenously into dogs in single or in repeated doses elicits hematic reactions characteristic of the macromolecular hematic syndrome (primary transitory leucopenia, secondary myeloid leucocytosis, anemia, accelerated erythrocytic sedimentation, increased clotting time).

The livers of such dogs show hydropic swelling and fatty infiltration of the liver cells and a negligible amount of glycogen. The aorta and the myocardial and renal arteries exhibit intimal and medial lesions of a proliferative and degenerative nature.

Repeated intravenous introduction of glycogen is not a harmless procedure.

AUTHOR.

Dauber, D. V., and Katz, L. N.: Experimental Atherosclerosis in the Chick. Arch. Path. **36**: 473, 1943.

Forty-three 3-month-old cockerels were divided into four groups. One group received liberal amounts of an adequate diet for six months. A second group received the same diet plus cottonseed oil. The third group was placed on restricted feeding, and the fourth group received 2 per cent cholesterol in cottonseed oil, added to the basic mash. Every cholesterol-fed chick acquired atherosclerosis of the thoracic and the abdominal aorta and of the major branches. Atherosclerosis of the splenic and the coronary arteries likewise resulted. The lesions showed accumulation of lipoid-containing foam cells, fibrosis, deposition of cholesterol crystals, calcification, and cartilage formation. No foam cell atheroma or calcification developed in any chick not fed cholesterol, but the cockerels not fed cholesterol showed a high incidence of intimal fibrosis of the abdominal aorta with or without lipoid.

It is, therefore, concluded that: Atherosclerosis with intimal thickening by accumulation of foam cells, fibrosis, calcification, and deposition of cholesterol can be produced in the omnivorous chick by cholesterol feeding. Feeding of cottonseed oil alone does not produce atheroma. Simple underfeeding will not cause vascular atheroma. The earliest spontaneous vascular lesion in the white Leghorn cockerel is intimal fibrosis of the abdominal aorta with and without lipoid. Foam cells enter the intimal vasa vasorum of the thoracic aorta in cholesterol-fed chicks. The working hypothesis advanced for the genesis of these lesions is applicable also to spontaneous atherosclerosis.

AUTHORS.

Bartlett, W. M., and Carter, J. B.: Combined Electrocardiography, Stethography and Cardioscopy in the Early Diagnosis of Heart Disease. Ann. Int. Med. **19**: 271, 1943.

Combined graphic and cardioscopic diagnosis in conjunction with the routine clinical examination constitutes a practical plan for the early recognition of heart disease.

The results of combined electrocardiography, stethography, and cardioscopy in the examination of 1,108 cases of heart disease are reported and discussed.

A simplified chest lead technique is described. Chest lead abnormalities occurred in 29 per cent of the cases. These abnormalities were directly proportional to the age of the patient, being found in 20 per cent of those between 31 and 41 years of age, and in 47 per cent of those between 61 and 87 years of age.

Organic heart murmurs are usually associated with heart sound abnormalities and often with changes in the electrocardiogram. Graphic methods are of value in differentiating organic and functional murmurs.

A diastolic murmur may be confused with a systolic murmur when the first heart sound is inaudible.

A stethogram is essential for the accurate diagnosis of gallop rhythm.

A stethogram differentiates a presystolic murmur from a "roughened" first sound.

In 88 per cent of 1,108 cases, clinical findings coincided with graphic findings.

In 12 per cent of 1,108 cases, the stethogram was essential for the diagnosis of gallop rhythm, of early mitral stenosis, or of early aortic disease.

Of 102 cases of gallop rhythm, 42 per cent were misjudged clinically so far as timing the extra sound was concerned.

A double-beamed cardioscope for the instantaneous visualization of stethogram and electrocardiogram is predicted as a diagnostic adjunct in the rapid examination of recruits, applicants for flight training and for insurance, and in screening for unrecognized heart disease.

Six typical cases are reported. Results of clinical examination, correlated with graphic findings, demonstrate the value of the method for the early diagnosis of heart disease.

Serial stethograms, like serial electrocardiograms, are useful in following the course of heart disease. A comparison of records from the same patient or from other cases with the same disease is frequently of value.

Cardioscopy as well as combined stethography and electrocardiography aids in teaching, since visual impressions are always superior to verbal descriptions.

This method of diagnosis is young but it will grow. Stethography has already arrived at a stage comparable to electrocardiography during the third decade of its development.

AUTHORS.

Joselevich, M.: Prolonged P-R Interval and Auricular Fibrillation. Rev. argent. de cardiol. **10:** 96, 1943.

Of nineteen cases of auricular fibrillation an electrocardiogram could be obtained showing sinus rhythm, the P-R interval measured more than 0.21 second in fifteen, and was normal in four.

Auricular fibrillation was persistent in eight and transient in eleven. Of the eight patients with chronic auricular fibrillation, three had mitral disease, three congestive heart failure, one had toxic goiter, and one had no demonstrable cardiac disease. Of the eleven patients with transient auricular fibrillation, one had Basedow's disease, one had syphilitic aortitis, one had pericardial effusion, one had myocardial infarction, and seven cases were of undetermined origin.

When the electrocardiogram showing normal sinus rhythm was obtained, nine patients were under digitalis treatment (eight had a prolonged P-R interval) two had recently been operated upon for a partial thyroidectomy (one had a prolonged P-R interval), and the only patient who was receiving quinidine showed also a prolonged P-R interval.

AUTHOR.

Hoff, H. E., and Nahum, L. H.: A Comparison of the Configuration in the Electrocardiogram of Endocardial and Epicardial Extrasystoles. Am. J. Physiol. **140**: 148, 1943.

The configuration, in Leads I and III of the electrocardiogram, of ventricular extrasystoles elicited by stimulation of points on the endocardium and the immediately opposite epicardium, has been studied.

The direction of initial deflections of endocardial and epicardial extrasystoles was the same in both Leads I and III over most of the surface of the heart. These regions included: (1) the area over the septum, both anterior and posterior; (2) an area on the lateral margin of each ventricle, which is referred to as the center of the ventricle because it is equidistant from the septal margins; and (3) the entire surface of the right ventricle.

The direction of initial deflections in Lead I of the epicardial and endocardial extrasystoles was also found to be the same over the entire posterior portion of the right ventricle and the anterior part of the left ventricle.

The direction of initial deflections in Lead III of epicardial and endocardial extrasystoles was the same over much of the posterior portion of the right ventricle and the anterior part of the left ventricle.

Two areas were found, of the anterior left ventricle toward the left lateral border and the posterior right ventricle toward the right lateral border, where the initial deflections of endocardial extrasystoles were opposite to those of extrasystoles from immediately overlying epicardial points.

These oppositely directed initial complexes of extrasystoles elicited from such regions of the endocardium were shown to arise, as do the similar complexes from stimulation of nearby epicardial points, from excitation of the opposite ventricle.

AUTHORS.

Riseman, J. E. F., and Smith, H. W.: Some Legal Aspects of Heart Disease and the Electrocardiogram. I. Nature and Volume of American Litigation Involving the Heart. Ann. Int. Med. **19**: 81, 1943.

The authors have endeavored in this paper to show what are the main sources of cardiac litigation, to point out basic legal principles important to the problem of proof, and to analyze type cases where electrocardiography might be used in court. In doing this, the authors have sought to stress important positive uses of the electrocardiogram while at the same time pointing out great variation in the probative value of the new species of evidence depending on the individual cardiac condition involved. They have stressed, as others have done, the interdependence of electrocardiographic interpretation on sound clinical examination and judgment. It is necessary to shatter any illusions that the electrocardiogram has universal diagnostic authority. It is only by recognizing the critical limitations of a new species of evidence that courts may protect against abuse and injustice likely to arise from extravagant claims regarding its virtue as proof.

AUTHORS.

Wilburne, M., and Langendorf, R.: The Significance of the Electrocardiogram With Prominent S Waves in Leads, I, II, and III. J. Lab. & Clin. Med. **28**: 303, 1942.

Electrocardiograms exhibiting prominent S waves (final inverted phase of the QRS complex measuring 25 per cent or more of the upright phase) in Leads I, II, and III were present in 84 cases of 1,850 consecutive electrocardiograms reviewed.

In 41 of these cases definite electrcardiographic abnormalities, such as left ventricular preponderance, right ventricular preponderance, combined right and

left ventricular strain, myocardial infarction, and nonspecific abnormal patterns were found. In eight others, questionable abnormalities were present.

In 35 cases no other deviations from the normal pattern were observed, and these were regarded as the otherwise normal S type of electrocardiogram. The criteria employed in this deduction are described. In nineteen of these cases no demonstrable heart disease was present; in three the clinical findings were inconclusive; and in thirteen there was clinical evidence of heart disease.

It is concluded that electrocardiograms exhibiting prominent S waves in Leads I, II, and III are more common in patients with evidence of heart disease than in normal persons in the population of an electrocardiographic laboratory. However, in an otherwise normal electrocardiogram the S type may be a normal variant, but before this decision is made the case should be thoroughly investigated.

AUTHORS.

Glazebrook, A. J.: Eisenmenger's Complex. Brit. Heart J. 5: 147, 1943.

A case presenting the clinical and radiographic features of the Eisenmenger complex is described, and the etiology and prognosis briefly described.

AUTHOR.

Saphir, O.: Myocarditis in Bronchiectasis. Arch. Int. Med. 72: 775, 1943.

A type of myocarditis occurs in patients with bronchiectasis. It was found at autopsy eight times among 152 patients and caused unexpected death three times. Clinically, myocarditis was diagnosed in only one instance. The most significant clinical observations in these patients was a discrepancy between the relatively slight elevation of temperature and the high pulse rate. Bronchiectasis with the incumbent severe inflammatory changes constitutes a primary focus to which myocarditis can be ascribed. Also in some patients with bronchial asthma who die suddenly, myocarditis may be a contributory cause of the sudden death. From this study it is clear that in many instances a correct diagnosis as to the presence or absence of myocarditis can be made only if many sections are cut from the myocardium and most carefully examined for the specific purpose of either finding or ruling out myocarditis.

AUTHOR.

Price, R. K., and Janes, L. R.: A Case of Subendocardial Infarction. Brit. Heart J. 5: 134, 1943.

A case of coronary arterial disease is described. It was observed to progress through the stages of angina pectoris, coronary insufficiency, and cardiac infarction to a fatal termination four months after the onset of symptoms. Detailed clinical and cardiographic evidence was obtained during life, and a careful examination of the heart was made after death. A type of infarct is described that may correspond to a muscle grouping in the ventricle rather than to the distribution of a main coronary vessel.

AUTHORS.

Koletsky, S.: Acquired Bicuspid Aortic Valve With Obliteration of the Commissural Raphe. Arch. Path. 36: 602, 1943.

The acquired bicuspid aortic valve with obliterated commissural raphe probably represents a further stage of the acquired bicuspid aortic valve with retracted horizontal raphe. In the four cases described, the obliterated commissure was identified by means of the aortic media-annulus fibrosus relationship.

The lesions are usually of rheumatic origin. Conclusive stigmas of rheumatic disease were found in the heart in three cases, while in one case there were probable stigmas, limited to the aortic valve.

In three cases the aortic valve showed calcific disease with stenosis. Bacterial endocarditis was present in two cases.

AUTHOR.

Shoun, A. N.: Rheumatic Heart Disease in Arizona. Southwestern Med. 27: 140, 1943.

The author reports on rheumatic fever and rheumatic heart disease in a limited area of southern Arizona. That rheumatic fever exists in Arizona as an endemic disease is not open to question. It is found in children who have been born and reared there and continues to occur in them as well as in those who come to Arizona with or without the disease. The report is based on a study of 690 children in the school population. Of these, there were 39 who showed some abnormality of the heart. An estimation is made of the number of cases of heart disease in the state, based on these figures. The author believes that heart disease in the areas in question is the same as in other centers throughout the country.

AUTHOR.

Camp, P. D., and Galvin, L. F.: Rheumatic Fever and Rheumatic Heart Disease in Virginia. Virginia M. Monthly 70: 397, 1943.

The authors review briefly certain available statistics from different parts of the country concerning the incidence of rheumatic fever and its mortality.

A survey was made by one of the authors, in 1940, on 979 children of school age in the city of Richmond. Four hundred and sixty-six of these children were white, and 513 were Negroes. Of the white group, 2.3 per cent presented findings of organic heart disease, whereas 8.5 per cent of the Negro group presented such evidence. These figures were in no way considered scientifically accurate, but merely served to indicate a general idea of the incidence of possible heart disease in such a group.

From May 1, 1940, to July 1, 1942, 254 children were referred to the State Rheumatic Fever Program Clinic for suspected rheumatic fever and heart disease. Of this group, a definite diagnosis of rheumatic fever or rheumatic fever heart disease was made on 97 cases, or 34.2 per cent. The diagnosis of possible and potential heart disease was made in 53, or 20.8 per cent.

During the year 1940-1941, the Medical College of Virginia Hospital Division admitted on all services a total of 22,968 cases. Of this number 193 cases, or 0.84 per cent, were diagnosed as rheumatic fever or rheumatic heart disease.

Symptoms and signs of the disease and method of diagnosis are reviewed. It is the impression of the authors that the manifestations of rheumatic fever in Virginia are frequently mild and indefinite, often requiring repeated examinations before a definite diagnosis can be made. Despite these mild manifestations, many cases develop severe unequivocal rheumatic heart disease in later life. In the authors' experience, initial attacks are often ushered in by gastrointestinal upsets with abdominal pain, nausea, emesis, and sometimes diarrhea. Nosebleeds are frequent. Subcutaneous nodules and erythematous rashes are relatively uncommon. Joint symptoms in the large majority of cases are either mild or absent altogether.

Treatment of the disease is briefly discussed. It is emphasized that it is just as important to promote a return to normal activity of those children with *inactive* rheumatic fever as it is to stress rest for those children manifesting active infection.

AUTHORS.

Decherd, G. M., Jr., and Herrmann, G. R.: Rheumatic Heart Disease in Texas. Texas State J. Med. **39**: 229, 1943.

The low and further decreasing incidence of rheumatic heart disease in the South and particularly in Texas seems to be substantiated in these studies.

Further surveys from the midwestern, southwestern, western, and northwestern areas of Texas seem highly desirable for the purpose of ascertaining those factors which alter the incidence, course, and prognosis of rheumatic disease there. Certainly, further studies are needed from the Gulf Coast and from the low altitude and high altitude areas of the Southwest in an attempt to identify the factors which mollify the disease here. The slight recent increase in the number of cases of rheumatic fever and heart disease seen in the diagnostic clinic, inaugurated in 1939, is most likely the result of increased state-wide interest.

AUTHORS.

McClendon, S. J.: Rheumatic Fever: Its Incidence in the Southwestern States. California & West. Med. **59**: 114, 1943.

A report based on a group of 112 proved cases of rheumatic fever studied in private practice, and an analysis of the information and reports on 83 additional cases admitted to one of the private hospitals in San Diego, California, is given. These patients were all children, ranging in age from 3 to 15 years. They were all native of southern California or southwestern Arizona, and had not resided outside that area at any time. The purpose of the study was to determine the type, severity, and season of onset, and the extent of cardiac damage in these patients.

Acute rheumatic fever and rheumatic carditis are found far more frequently in southern California than has been claimed by most observers. The incidence can be charted more accurately if laws requiring reportability of the disease are systematically observed.

The severity of the cardiac complications is approximately as great as in colder and more severe climates. Poor housing and economic conditions do not seem to be contributory factors to the disease in this area. Repeated respiratory and throat infections of a streptococcic type seem to precede the actual onset of the acute attack. The removal of tonsils and adenoids does not seem to alter the incidence of the disease nor act as a prophylaxis.

AUTHOR.

Dressler, M., and Silverman, M.: Cardiovascular Syphilis: An Approach to Early Clinical Recognition and Early Treatment. Ann. Int. Med. **19**: 224, 1943.

Of 1,270 cases of proved syphilis studied, 24 per cent were diagnosed clinically as uncomplicated aortitis, and 30.7 per cent as cardiovascular syphilis as a whole. Of the latter group, 78 per cent were cases of uncomplicated aortitis. The proportion of males to females was approximately two to one, and that of the white to the Negro race approximately the same.

The criteria for the physical diagnosis of uncomplicated aortitis are presented and discussed, and are found of value in patients 40 years of age or younger. It is more common in the Negro than in the white race in this age group.

The high percentage (47.4 per cent) of hypertension among the cases of cardiovascular syphilis studied is not purely coincidental. No valid reason is advanced for its presence.

Uncomplicated aortitis is more common among congenital syphilitics than has been reported before.

Of 128 cases of cardiovascular syphilis that remembered the chancre, uncomplicated aortitis was diagnosed in 38 cases within ten years after the primary infection.

Uncomplicated aortitis is a symptomless disease. Hints on physical diagnosis were discussed.

Neurosyphilis was present in 26.6 per cent of the cases of cardiovascular syphilis.

Fluoroscopy and roentgenography are of value in corroborating the clinical diagnosis. Uncomplicated aortitis can be diagnosed clinically in normal-sized aorta.

An outline of treatment is presented.

AUTHORS.

Cooke, W. T., and Cloake, P. C. P.: Extreme Cardiac Hypertrophy: Report of Two Cases With Aortic Hypoplasia and Endocrine Disorders. Brit. Heart J. 5: 139, 1943.

Two cases of extreme cardiac hypertrophy are reported.

In the first, a male diabetic, aged 33 years, the heart weighed 1,350 grams. There was no associated valvular disease and only moderate increase in the size of the heart chambers. The descending part of the thoracic and abdominal aorta showed moderate hypoplasia. No definite cause for this extreme cardiac hypertrophy could be found, but there was evidence of thyrotoxicosis, and it is suggested that pituitary hyperfunction played some part.

In the second, a female acromegalic, aged 35 years, the heart weighed 900 grams. The hypertrophy affected the left ventricle predominantly and was associated with an interauricular septal defect and hypoplasia of the aorta. The pituitary dysfunction was thought to have played the chief part in the production of the enlargement in this case.

AUTHORS.

Pickering, G. W.: The Circulation in Arterial Hypertension. Brit. M. J. 2: 1, 31, 1943.

This article is an abridged version of the Oliver-Sharpey Lectures delivered at the Royal College of Physicians of London, in 1943. It is an important outline and résumé of present knowledge concerning the nature of hypertension and its effect on the circulation in general.

MCCULLOCH.

Foà, P. P., Foà, N. L., and Peet, M. M.: Arteriolar Lesions in Hypertension: A Study of 350 Consecutive Cases Treated Surgically. An Estimation of the Prognostic Value of Muscle Biopsy. J. Clin. Investigation 22: 727, 1943.

The ratio of the thickness of the wall to the diameter of the lumen (W/L) of the arterioles in skeletal muscle was computed from data obtained by direct measurement of the blood vessels in biopsy material. Three hundred and fifty consecutive cases of arterial hypertension were studied. All the patients were subsequently submitted to supradiaphragmatic splanchnicectomy and lower dorsal sympathetic ganglionectomy, and were followed for nine months to seven years after operation. The degree of thickening of the arteriolar wall was compared to the severity of other signs and symptoms and to the therapeutic results. Patients with more severe thickening of the arteriolar wall had more severe symptoms, showed poorer therapeutic results and greater mortality. The correlation is particularly significant between arteriosclerosis and other evidence of damage to the vascular system, such as the elevation of the blood pressure. The results show that the determination of W/L in skeletal muscle adds very significant information to the clinical and pathologic picture of hypertension. It is important in the prognosis of the disease. The results are in agreement with the hypothesis that the surgical treatment of hypertension described here gives better results when hypertension is due to a spasm of the arterioles or to a mild, reversible degree of hypertrophy of the muscle fibers in the

media, and not when severe permanent anatomic lesions have transformed the majority of the arterioles into narrow and rigid tubes.

It is suggested that the study of hypertensive patients should include, whenever possible, the determination of the intensity of the vasomotor reactions, the measurement of the effective renal blood flow by diodrast clearance, the observation of the blood vessels of the eye grounds, and the determination of the wall/lumen ratio of the arterioles in muscle biopsies. This direct investigation of the vascular system is at least as important as the examination of the heart and of the renal function, which reveals the extent of the damage produced by hypertension to vital organs and functions, rather than the severity of the disease itself and the extent to which vascular lesions have become irreversible.

AUTHORS.

Massie, E., and Miller, W. C.: The Heart Size and Pulmonary Findings During Acute Coronary Thrombosis. Am. J. M. Sc. **206**: 353, 1943.

The change in heart size in sixteen patients following unequivocal acute coronary thrombosis was studied by teleoroentgenograms taken over periods extending from twelve hours to seven months following the acute attack.

No consistent change in cardiac size or shape was noted in this study. Eight of the patients showed no change in any of their entire series of films. Each of four other patients presented only one film with cardiac measurements significantly different from the others of their respective series, and these were taken at greatly varying intervals (three days to three months) after the attack, with both increasing and decreasing measurements occurring. It is noteworthy that, in the important first two weeks following the acute accident, only four cases of the entire series had a change in cardiac measurements; in two they were increased, and in the other 2 they were decreased.

It is impossible to state from this study that there is any significant feature which characterized the eight patients who showed a change in cardiac size following coronary thrombosis. Nevertheless, the more frequent occurrence of complications within this group attracts attention. Aside from these complications, it appeared that the patients with significant change in cardiac size were somewhat more ill than the others.

The findings in the roentgen ray films of pulmonary congestion in the first and second weeks following the coronary accident were especially noteworthy. Twelve patients showed roentgenologic evidence of such pulmonary involvement, whereas, in only seven of these, did auscultation reveal the presence of basal râles. In four patients, evidence of pulmonary congestion was lacking on both roentgen ray and physical examination.

AUTHORS.

Altschule, M. D., Zamcheck, N., and Iglauer, A.: The Lung Volume and Its Subdivisions in the Upright and Recumbent Positions in Patients With Congestive Failure. Pulmonary Factors in the Genesis of Orthopnea. J. Clin. Investigation **22**: 805, 1943.

Studies of the subdivisions of the lung volume were made in twelve patients with congestive failure in the sitting and recumbent positions.

No increase in the degree of pulmonary congestion was demonstrated in recumbency in orthopneic patients.

A cephalad shift of the diaphragm occurs in recumbency; this causes changes in respiration and circulation which tend to increase dyspnea.

The complexity of interrelated factors which are related to the genesis of the orthopnea of congestive failure is discussed.

AUTHORS.

Starr, I.: Clinical Studies on Incoordination of the Circulation as Determined by the Response to Arising. J. Clin. Investigation 22: 813, 1943.

The response of the circulation when the subject arose, as determined by the ballistocardiograph, has been employed as a test of its coordination, i.e., of the ability to adapt the cardiac output to the needs of the moment.

Normal standards for circulatory coordination have been determined by a statistical analysis of the results of 120 tests made on 75 healthy young adults, before and after arising. Over 150 patients have been studied also.

In healthy persons, the physiologic adjustment necessitated by assuming the erect position is largely accomplished by the basomotor mechanism, and the cardiac output changes but little.

In many sick persons, the circulation changes much more, and the abnormality may be in either direction. In the commoner type, the circulation is unduly increased on arising, as if the vasomotor responses were insufficient to support the blood pressure unaided. This type is found with great frequency in many types of disease. In the much rarer type, the circulation abnormally diminishes on arising.

Many weakened patients cannot stand without involuntary muscular movements of the lower extremities. Such movements are always called forth in persons subjecting to fainting before they collapse, and they seemed designed to support the circulation. The authors regard their presence as evidence of the inadequacy of the vasomotor and other circulatory responses to maintain blood pressure.

Patients with symptoms referable to their circulation without detected organic disease, the group often diagnosed as neurocirculatory asthenia, show incoordination of the circulation in a large majority of cases. The frequency of such incoordination in many conditions of disease is suggested as the reason for the widespread occurrence of the symptoms these patients exhibit, such as undue breathlessness on exertion, faintness, dizziness, and the like.

AUTHOR.

Dexter, L., Frank, H. A., Haynes, F. W., and Altschule, M. D.: Traumatic Shock. VI. The Effect of Hemorrhagic Shock on the Concentration of Renin and Hypertensinogen in the Plasma in Unanesthetized Dogs. J. Clin. Investigation 22: 847, 1943.

A study has been made of the renal humoral pressor mechanism, in unanesthetized dogs in shock, from the removal of 4 to 5 per cent of the body weight of blood.

It is confirmed that readily detectable amounts of renin appear in the circulating plasma.

The concentration of hypertensinogen in plasma decreases in severe hemorrhagic shock, sometimes to extremely low levels. Since, in shocked dogs which have been nephrectomized, the concentration of hypertensinogen remained unchanged or increased, it is assumed that its diminution in shocked dogs with intact kidneys is due mainly or solely to the presence of excessive amounts of renin.

Transfusion of 4 to 5 per cent of body weight of whole blood, with nearly normal titer of hypertensinogen, did not increase the concentration of hypertensinogen in plasma appreciably, presumably due to its almost immediate conversion to hypertensin by the large amount of circulating renin.

The renal humoral pressor mechanism is considered to represent a compensatory measure, on the part of the body, to maintain normal blood pressure in dogs rendered hypotensive by hemorrhage.

This mechanism functions inadequately, however, due to the inability of the organism to synthesize hypertensinogen as rapidly as it is converted to hypertensin by the large excess of circulating renin.

AUTHORS.

Steinberg, M. F., Grishman, A., and Sussman, M. L.: Angiocardiography in Congenital Heart Disease. II. Intracardiac Shunts. Am. J. Roentgenol. **49**: 766, 1943.

Sixty-five congenital cardiacs have been subjected to angiocardiography. Eighteen cases represented various types of intracardiac shunts. The method usually demonstrated the shunt when a right-to-left shunt existed and sometimes when it was produced by the injection. In other cases, when the shunt was left-to-right, reopacification of the right heart could be made out occasionally. In all cases, the demonstration of the pathologic anatomy and physiology present was of value in differential diagnosis. It is likely that with additional data better evaluation of prognosis will be possible.

AUTHORS.

Shapiro, R.: "Mitralization" of the Cardiovascular Silhouette in the Posteroanterior Roentgenogram. Am. J. Roentgenol. **50**: 46, 1943.

The term "mitralization," as applied to the cardiovascular silhouette in the posteroanterior roentgenogram, is used to signify a straightening or convexity of the left upper heart border.

The so-called "mitral type" heart may be produced by many different factors or conditions, and is not pathognomonic of a mitral valvular lesion.

The roentgenologic diagnosis of mitral stenosis should not be made from a posteroanterior roentgenogram alone. Oblique views, especially the right anterior oblique view with barium paste in the esophagus, should be taken to demonstrate the presence of left atrial enlargement. The finding of left atrial enlargement tends to favor a diagnosis of mitral valvular disease, although such enlargement may also occur in other cardiac lesions.

The roentgenologist should discard such ambiguous terms as "mitralization," "mitral type heart," "mitral configuration," etc., since they only tend to be confusing and inaccurate.

AUTHORS.

Murray, G.: Aortic Embolectomy. Surg., Gynec. & Obst. **77**: 157, 1943.

A report of five successful aortic embolectomies is given. In all five cases there were no technical difficulties and no accidents or disasters. An extraperitoneal abdominal approach gives a satisfactory exposure through which the operation can be carried out without difficulty. The circulation was restored and the impending gangrene of both legs in each case was immediately replaced by extremities with normal circulation and function. In spite of the fact that most of these cases eventually die of embolism, the patient can be completely relieved of symptoms and return to the original state of health, following surgical treatment of the immediate episode.

AUTHORS.

Haney, H. F., Lindgren, A. J., Karstens, A. I., and Youmans, W. B.: Responses of the Heart to Reflex Activation of the Right and Left Vagus Nerves by the Pressor Compounds, Neosynephrin and Pitressin. Am. J. Physiol. **139**: 675, 1943.

The pressor compounds neosynephrin, pitressin, and angiotonin are capable of producing an inhibition of the heart which is best explained on the basis of reflexes initiated in response to the rise of blood pressure resulting from their vasoconstrictor action. Administration of these pressor compounds may be said to result in a physiologic activation of the vagus nerves.

In experiments on dogs whose right vagus has been cut and whose left vagus remains intact, i.e., left vagus dogs, the response to the pressor compounds commonly includes A-V heart block. Thus, in this group of animals, A-V block followed the injection of neosynephrin in 27 of 37 experiments on fourteen dogs, of pitressin in 7 of 10 experiments on seven dogs, and of angiotonin in a single experiment.

I dogs whose left vagus had been cut and whose right vagus remained intact, i.e., right vagus dogs, no instances of A-V heart block occurred in response to injection of neosynephrin in 28 experiments on twelve dogs, of pitressin in 12 experiments on six dogs, and of angiotonin in a single experiment.

Physiological activation of either the right or the left vagus results in sinus bradycardia. No remarkable difference in the degree of heart slowing produced by the left as compared with the right vagus is evident.

As a result of physiologic activation of the right vagus, the automaticity of the S-A node frequently is depressed to a level at which the A-V node takes over the function of pacemaker. Thus, A-V nodal rhythm was observed in 4 of 28 experiments using neosynephrin, and in 1 of 12 experiments using pitressin. A-V nodal rhythm occurred in none of the experiments involving the left vagus group of dogs.

The completely denervated heart of the dog is not depressed by neosynephrin in the doses in which it was employed.

In the majority of experiments, pitressin fails to cause significant inhibition of the completely denervated heart. When inhibition occurs, it is usually of small degree.

AUTHORS.

Chen, K. K., Elderfield, R. C., Uhle, F. C., and Fried, J.: Synthetic Glycosides of Digitoxigenin, Digoxigenin, and Periplogenin. J. Pharmacol. & Exper. Therap. **77:** 401, 1943.

Six synthetic glycosides, namely, digitoxigenin-β-, digitoxigenin-β-tetraacetyl-, digoxigenin-β-, digoxigenin-β- tetraacetyl-, periplogenin-β-, and periplogenin-β- tetraacetyl-α-glucosides, have been studied pharmacologically and compared with their corresponding natural glycosides and aglycones—digitoxin, digitoxigenin, digoxin, digoxigenin, periplocymarin, and periplogenin.

In cats, digitoxigenin-, digoxigenin-, and periplogenin-β-α-glucosides are more powerful than digitoxin, digoxin, and periplocymarin, respectively. All the tetraacetyl derivatives have a low potency.

In frogs, the results are less uniform. While digitoxigenin- and digoxigenin-β-α-glucosides are more active than digitoxin and digoxin, respectively, periplogenin-β-α-glucoside is weaker than periplocymarin. There is also suggestion that digoxigenin-β-tetraacetyl-α-glucoside is more active than digoxigenin.

Periplogenin is decidedly less potent than periplocymarin, indicating the favorable influence of the sugar component in the molecule of the glycoside.

AUTHORS.

Finch, C. A., and Marchand, J. F.: Cardiac Arrest by the Action of Potassium. Am. J. M. Sc. **206:** 507, 1943.

Two cases of fatal potassium poisoning have been described. In one, there was a spontaneous accumulation of the serum potassium to 8.85 meq./l and a further elevation to 10.50 after an oral dose of 4.5 Gm. of the chloride. The other had been given large therapeutic doses for five days. In each there was a failure of renal excretion.

The diagnosis was made by comparison of the findings in these cases with those reported in experimental potassium poisoning, including the serum and urine potas-

sium levels (Case 1), the electrocardiogram, and the clinical course. The relationship of paralysis and of renal failure to potassium poisoning was discussed, and the electrocardiographic changes leading to arrest of the heart have been shown and described.

The parallel features of these two cases illustrating the clinical course of human potassium poisoning were the result of the combined effect of the potassium poisoning and the underlying disease. In each there was: (a) an acute uremia with oliguria; (b) recurrent nausea and retching; (c) episodes of bradycardia unaccompanied by symptoms of cardiac failure or changes in blood pressure; (d) a sudden ascending flaccid quadriplegia without paralysis of the trunk or disturbance of speech or mental functions; (e) electrocardiographic changes including elevated T waves, absent P waves, intraventricular block, and terminal irregularities of the rhythm; (f) arrest of the heart in diastole prior to the cessation of respiration.

AUTHORS.

Forster, R. E., II.: The Medical Use of Thiocyanates in the Treatment of Arterial Hypertension. Am. J. M. Sc. **206**: 668, 1943.

The majority of clinical workers believe that thiocyanate has a definite hypotensive effect in the arterial hypertensive patient. However, this hypotensive effect has not been demonstrated in the laboratory. The mechanism by which this clinical blood pressure drop occurs is not known. It is to be hoped that a complete statistical analysis will be done in the future to prove this suspected hypotensive effect.

A satisfactory method for the administration of thiocyanate has been suggested by Barker, which will give minimal toxicity if handled correctly. Thiocyanate should never be given without blood levels being taken. Thiocyanate is not a blanket cure-all for "hypertension" and should be used only in selected cases and where no contraindication exists.

Any relief of subjective symptoms bears minimal relation to the blood pressure drop.

AUTHOR.

Book Review

MODIFICAÇOES DE FORMA DO ELETROCARDIOGRAMA: By Dr. Dante Pazzanese, Chefe das Clinicas Cardiologicas do Hospital Municipal de São Paulo e do Servico Cirurgico do Professor B. Montenegro, Grafica da Prefeitura, São Paulo, 1942, 373 pages, 247 illustrations.

This new book on electrocardiography has distinctive features. Essentially, it is divided into two parts: The first describes the changes in the various electrocardiographic waves; it is, therefore, a theoretical study. The second describes electrocardiographic changes in various diseases, and is, therefore, an applied study with practical aims.

Each chapter has a short introduction; this is followed by a discussion of the tracings, and then by a summary in both Portuguese and English. The book contains a detailed and up-to-date review of the literature. Most of the tracings are original, and they are usually clear and typical.

Some aspects of this book might be considered either virtues or defects, according to the point of view of the reader. The dogmatic and strongly worded expression of personal views and the detailed and laborious quotation of too many authors are among them.

Some chapters, such as that on electrocardiographic changes in infectious and parasitic diseases, and that on acute accidents and "agony of the heart," will be useful for reference, and are more complete than in other, similar books.

The translation of the summaries into English is adequate.

Dr. Pazzanese has written an interesting and valuable book which should have a place in the library of any cardiologist.

ALDO LUISADA.

Erratum

In the article entitled "On Certain Applications of Modern Electrocardiographic Theory to the Interpretation of Electrocardiograms Which Indicate Myocardial Disease," by Robert H. Bayley, which appeared in the December, 1943, issue of the JOURNAL, volume 26, page 808, the second sentence in the second paragraph should read: "The vector G is known as the manifest mean electrical axis of QRST, or as the gradient, which may be said to point from regions in the ventricular muscle at the epicardial and endocardial surfaces in which the average duration of the excited state is greatest, toward regions in the muscle at these surfaces where the average duration is least."

American Heart Association, Inc.

1790 Broadway at 58th Street, New York, N. Y.

THE American Heart Association is the only national organization devoted to educational work relating to diseases of the heart. Its activities are under the control and guidance of a Board of Directors composed of thirty eminent physicians who represent every portion of the country.

A central office is maintained for the coordination and distribution of important information. From it there issues a steady stream of books, pamphlets, charts, films, lantern slides, and similar educational material concerned with the recognition, prevention, or treatment of diseases of the heart, which are now the leading cause of death in the United States. The American Heart Journal is under the editorial supervision of the Association.

The Section for the Study of the Peripheral Circulation was organized in 1935 for the purpose of stimulating interest in investigation of all types of diseases of the blood and lymph vessels and of problems concerning the circulation of blood and lymph. Any physician or investigator may become a member of the section after election to the American Heart Association and payment of dues to that organization.

The income from membership and donations provides the sole financial support of the Association. Lack of adequate funds seriously hampers more intensive educational activity and the support of important investigative work.

Annual membership is $5.00. Journal membership at $11.00 includes a year's subscription to the American Heart Journal (January-December) and annual membership in the Association. The Journal alone is $10.00 per year.

The Association earnestly solicits your support and suggestions for its work. Membership application blanks will be sent on request. Donations will be gratefully received and promptly acknowledged.

**Executive Committee.*